In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 17-250V

(to be published)

* *	Chief Special Master Corcoran
NEONA MARTIN, *on behalf of the ESTATE OF JOSEPH JAMES MARTIN*, *	
*	Filed: July 17, 2020
Petitioner, *	
v. *	Influenza vaccine; Death; Pathology findings; Bacterial respiratory infection; Cytokine production; Non-infectious inflammation; Timeframe
SECRETARY OF HEALTH AND HUMAN SERVICES, *	
Respondent. *	
* *	

Milton Clay Ragsdale, IV, Ragsdale LLC, Birmingham, AL, for Petitioner.

Catherine Stolar, U.S. Dep't of Justice, Washington, DC, for Respondent.

ENTITLEMENT DECISION[1]

On February 21, 2017, Neona Martin, on behalf of the estate of Joseph Janes Martin (her deceased husband), filed a petition seeking compensation under the National Vaccine Injury Compensation Program ("Vaccine Program").[2] Petitioner alleged that Mr. Martin died on February 26, 2015, as a result of an influenza ("flu") vaccine he received on February 5, 2015. Petition (ECF No. 1) at 1. An entitlement hearing in the matter was held February 3–4, 2020 in Washington, D.C.

For the reasons stated in greater detail below, I deny an entitlement award in this matter. Petitioner has not established that Mr. Martin's death three weeks post-vaccination more likely

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[1] This Decision will be posted on the Court of Federal Claims' website in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012)). **This means that the Decision will be available to anyone with access to the internet.** As provided by 42 U.S.C. § 300aa-12(d)(4)(B), however, the parties may object to the Decision's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has fourteen days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the whole Decision will be available to the public. *Id*.

[2] The Vaccine Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3758, codified as amended at 42 U.S.C. §§ 300aa-10 through 34 (2012) [hereinafter "Vaccine Act" or "the Act"]. Individual section references hereafter will be to § 300aa of the Act (but will omit that statutory prefix).

than not was caused in any part by the flu vaccine, or that the vaccine *could* be fatal in the manner alleged. The tragedy of his sudden death is far more likely attributable to his pre-vaccination health condition, and/or an intercurrent bacterial lung infection that went undiagnosed until after his death.

I. Factual Background

Mr. Martin's Pre-Vaccination Condition

Mr. Martin, a retired Army veteran, was 53 years old when he received the flu vaccine at a Veterans Affairs ("VA") facility in Huntsville, Alabama, on February 5, 2015. Ex. 1 at 1; Ex. 5 at 115-16; Ex. 9 at 1. He was not in good health at the time, and suffered from a number of comorbidities – in particular a history of poorly-controlled diabetes mellitus. His diabetes had caused secondary diabetic neuropathy and retinopathy, as well as a diabetic foot ulcer in 2014. Ex. 5 at 1–243, 611–63; Ex. 7 at 178–485. Mr. Martin's past medical history also included hypertension, hyperlipidemia, chronic diarrhea, service-related disabilities, and kidney disease. Ex. 5 at 1–243, 611–63; Ex. 7 at 178–485.

In addition to the above, the record establishes that Mr. Martin had recently begun having syncopal episodes. Thus, on December 12, 2014 (about ten weeks before his death), Mr. Martin went to the Huntsville Hospital emergency room after a syncopal episode at a gun range, where he reported that he "woke up [o]n the floor," with "no idea what [had] happened." Ex. 7 at 204. Mr. Martin also noted at this time that he had been experiencing similar episodes over the prior three weeks. *Id.* At the ER, Mr. Martin had a normal CT scan but an abnormal EKG, plus a high glucose reading. *Id.* at 205, 208, 224. Indeed, the EKG determination included the finding "septal infarct, age undetermined"—which suggested the possibility that Mr. Martin had previously suffered an undiagnosed heart attack sometime in the past. *Id.* at 224.[3]

At a later doctor's visit in January 2015 at the Birmingham VA Hospital, Mr. Martin's primary care physician ("PCP") confirmed Mr. Martin's ongoing diabetes and notably high glucose levels, which were at that time measured at 414 mg/dl—well in excess of the normal range (70–110 mg/dl). Ex. 5 at 129–30. Mr. Martin also reported some recent incidents of chest pain, and he displayed an increased heart rate that treaters deemed the product of dehydration attributable to "uncontrolled diabetes." *Id.* at 128.

The following month, on February 3, 2015, Mr. Martin had a telehealth consultation with a VA nurse for his diabetes. Ex. 5 at 123–25. Two days later, on February 5, 2015, he followed up with his PCP, who deemed Mr. Martin "in complete denial of his disease." *Id.* at 112, 113–22. At that time, Mr. Martin continued to have dizziness, but reported no further

[3] As one of Respondent's experts, Dr. Kathleen Collins, noted at hearing, "septal infarction . . . is another word for a heart attack." Tr. at 299.

episodes of syncope. *Id*. at 118–20. It was at that follow-up visit that Mr. Martin received the flu vaccine in question. *Id*. at 115–16.[4]

The parties dispute whether the flu vaccine was contraindicated for Mr. Martin. Petitioner has maintained that it was, but relies on a hospital record prepared after Mr. Martin's death. Ex. 7 at 154. This particular record thus does not shed light on whether, *as of the time the vaccine was administered*, Mr. Martin's PCP had such concerns (and does not elaborate on how or why this alleged contraindication came up at this time). By contrast, the record from the February 5, 2015 date of vaccination states that Mr. Martin verbally "*denie[d]* contraindications to the influenza vaccine," including any prior allergic reaction to egg protein. Ex. 5 at 115 (emphasis added). In addition, it appears from the filed record that Mr. Martin had received the flu vaccine in previous years, without complaint or reported reaction. *See, e.g., id.* at 241–43 (flu vaccine administered in October 2013, after Mr. Martin verbally denied contraindications). I ultimately find that the record preponderates against a determination that the flu vaccine was contraindicated by any medical treater, although my overall analysis does not turn on this fact.[5]

February 2015 and Circumstances of Mr. Martin's Death

There are few records for the period between the date of vaccination and the days immediately prior to Mr. Martin's death. There is no independent record evidence that Mr. Martin experienced an immediate reaction to the February 2015 vaccination, or any arguably-related symptoms within a few days later. The last medical record created before the date of Mr. Martin's death is a February 24, 2015 telemedicine nurse consultation note regarding his uncontrolled diabetes. Ex. 5 at 101–10. (It appears from these records that Mr. Martin could remotely transmit blood sugar readings to VA treaters for monitoring, and could also communicate with caregivers by phone). But nothing in these records disclose Mr. Martin's condition at the time (beyond his blood sugar readings), or whether his overall health was different in tenor from what he had previously experienced. *Id.* at 101–22. Indeed, Mr. Martin appears to have been asked some questions about his functionality or health problems as part of the February 24th telemedicine consultation, but identified no recent flare-ups. *Id.* at 108–09.

Petitioner, however, has alleged in witness statements filed in this case that within three to five days after receiving the vaccine at issue, Mr. Martin "became ill" with "flu-like symptoms," including "chills, headaches, body aches, dizziness, weakness, diarrhea, nausea and vomiting." *See* Ex. 10 (Affidavit of Neona Martin, dated November 17, 2017 (ECF No. 13-1)) at 1. Petitioner also proposes that in this time period Mr. Martin "likely experienced a fever, based

[4] According to the medical records Mr. Martin received the inactivated influenza vaccine. Ex. 5 at 115. At the time of injection Mr. Martin was counseled on regarding precautions, risks, and benefits of the vaccine. *Id.* He also received the "CDC Influenza Vaccine (Inactivated/IIV) Information Statement 2014-2015." *Id.*

[5] Petitioner has also not offered evidence in this case to establish that the flu vaccine is *generally* contraindicated for persons with diabetes. In fact, evidence filed in this matter supports the contrary.

on the chills and sweating episodes I observed," complained of feeling worse than he had before, and that these symptoms progressed to the date of his death. *Id.* She further explains that Petitioner's ability to see a doctor in some of this time period was limited due to hazardous winter travel conditions for the area in which they lived. *Id.*

On February 26, 2015, at 4:49 a.m., Mrs. Martin called 911 after finding Mr. Martin unresponsive, pulseless, and apneic in their bathroom. Ex. 6 at 3–7; Ex. 5 at 482. In subsequently-created witness statements as well as in contemporaneous reports to emergency first responders, Petitioner has maintained that Mr. Martin had not recently felt well, told her early on the morning in question he felt dizzy and was coughing, then went to the bathroom where she found him a few minutes later. Ex. 10 at 1, Ex. 6 at 7, Ex. 7 at 10. She specified in subsequent hospital records that Mr. Martin had been experiencing cold symptoms for a few days prior to this incident. Ex. 7 at 10; *see also* Ex. 5 at 342–43 (patient was sick with cold for "few days" with "recent cold symptoms"); Ex. 5 at 405 ("[w]ife said that [Mr. Martin] woke up feeling dizzy, went to the bathroom . . . Wife said that he has been sick w/ cold for days").

Mrs. Martin attempted to perform CPR while waiting for EMS personnel to arrive. Ex. 6 at 3–7. When such personnel arrived at 5:07 a.m., Mr. Martin remained unresponsive, pulseless, and apneic. *See id*.; Ex. 5 at 340–41; Ex. 7 at 10–11. EMS attempted to resuscitate Mr. Martin, which required suctioning vomit out of his airways, then took him to Huntsville Hospital emergency room. Ex. 6 at 3–6, 7. EMS records deemed Mr. Martin's breathing apneic. *Id.* at 4. Upon arrival, it was determined that Mr. Martin's blood glucose level was 671 mg/dL (far higher than his also-elevated reading the month before). Ex. 5 at 432. ER records reported that Mr. Martin had suffered cardiac arrest. Ex. 7 at 9.

A battery of labs diagnostics were performed on Mr. Martin. *See* Ex. 7 at 10. For example, his temperature on arrival was 92.5 degrees, his heart rate swung from 80 bpm and 111 bpm between periods of pulselessness, and his blood pressure fluctuated from high to low. *Id.* Chest X-rays showed Mr. Martin had pneumonia in the upper right lobe of his lungs. *Id.* And his white blood cell count was notably elevated (a 19.8 reading, in comparison to normal values of 4.8 to 10.8). Ex. 5 at 437.

While in the ER, Mr. Martin experienced several additional episodes of cardiac arrest with asystole and, following multiple resuscitation attempts, was pronounced dead at approximately 9:30 a.m. on February 26, 2015. Ex. 4 at 1; Ex. 5 at 323, 340; Ex. 7 at 6, 10, 48–49; Ex. 8 at 1. The treating physician proposed that the cause of Mr. Martin's cardiac arrest was unknown, but that it was "likely secondary to sepsis due to pneumonia versus undiagnosed coronary artery disease with history of diabetes mellitus." Ex. 5 at 341; Ex. 7 at 11. The death certificate identifies the cause of death as "cardiac arrhythmia." Ex. 4 at 1.

Autopsy Report

An autopsy was performed the next day (February 27, 2015) by Dr. L. Allen Perkins, a pathologist at Huntsville Hospital. *See generally* Ex. 8. Dr. Perkins noted that Mr. Martin's airways were clear of debris and foreign material. He also observed "fungal organisms highlighted on GMS special stain associated with food particles most likely secondary to agonal aspiration" (meaning gasping at the time of death), although he deemed these findings postmortem in nature rather than part of the etiology of Mr. Martin's death. *Id.* at 1, 4.

In addition, Dr. Perkins took tissue from the lung and sent it to a laboratory, but found an absence of "significant histopathologic abnormality." Ex. 8. at 4. However, he did observe neutrophilia within the airways of both lungs. *Id.* From this, Dr. Perkins listed bilateral bronchopneumonia as the first part of his pathological diagnosis, emphasizing it in his summary as well, although his report did not ultimately designate it as his primary conclusion. *Id.* at 1. The pathology report did not otherwise propose that the flu vaccine Mr. Martin received three weeks or so prior was causal of his death—nor did any other of the medical treaters who attended to him on February 26th.

II. Expert Witness Testimony

A. *Petitioner's Experts*

1. <u>Dr. Alan Levin</u> – Dr. Levin, an immunologist with some pathology training, was Petitioner's first expert to testify at trial, and also offered two expert reports. Tr. at 33–104; Report, dated November 27, 2017, filed as Ex. 11 (ECF No. 13-2) ("Levin Rep."); Report, dated November 14, 2018, filed as Ex. 23 (ECF No. 21-3) ("Levin Supp. Rep."). He opined that Mr. Martin's health issues made him susceptible to an aberrant innate immune response, leading to and causing his death. Tr. at 35. That response was driven by the flu vaccine, and mediated through what Dr. Levin deemed a "noninfectious inflammatory process." *Id.* at 93.

Dr. Levin is a board-certified immunologist and pathologist. Levin CV at 1–2, filed Nov. 27, 2017, as Ex. 12 (ECF No. 13-3); Tr. at 34. He earned his B.S. in Chemistry from the University of Illinois, Champaign-Urbana in 1960, his M.S. in biochemistry from the University of Illinois in 1963, and his M.D. from the University of Illinois in 1964. Levin CV at 1. In 1995, however, Dr. Levin earned his J.D. from Golden Gate University. *Id.* Dr. Levin now spends most of his time on the practice of law—about 95 percent of his time since the mid-1990s. Tr. at 54–55 He has not taught medicine or pathology in over 20 years and focuses on environmental toxicology. *Id*. at 59. Dr. Levin is not boarded in anatomic pathology, but performed an autopsy about three years ago and "reviews histological slides on a regular basis." *Id*. at 61–62. He regularly testifies as a Program expert, but admitted that one of his opinions had been excluded in a civil case outside the

Vaccine Program.[6] *See also Id*. at 64 (Dr. Levin admitting that a federal district court judge had referred to him as a "junk scientist").

The scientific basis for Dr. Levin's opinion was rooted in the nature of the immune response that vaccines engender. The body's immune system is best understood, he maintained, as a "mechanism of biological response modification," and includes several arms. Tr. at 37, 38. There is the initial innate response, followed by an adaptive response. *Id.* at 38. For healthy individuals, the innate response is usually thought not to be "antigen-specific" (meaning reactive to the specific antigen of the presenting wild virus or vaccine), although Dr. Levin observed that science was beginning to see that the initial response does have the capacity to "remember" subsequent presentations of a previously-encountered antigen and to react accordingly. *Id.* at 41. The subsequent adaptive response, however, is well-understood to be more directed at the antigen in question, and through vaccination can be "trained" to look for and attack foreign antigens to which it has been previously exposed. *Id.* at 42.

In Dr. Levin's view, the immune system's response to both wild infections and vaccines will invariably involve cytokines—messenger immune cells. Tr. at 35–36, 38. The cytokines that react to a wild infection or vaccine, he reasoned, also cause symptoms through inflammation that can make a person feel unwell (i.e. fever, aches, malaise, etc.). *Id.* at 38. This response is worsened, and more dangerous, in susceptible individuals. *Id.* at 39. Although some such individuals might not find that a vaccine creates any ill-feeling, for others it will produce an overreaction resulting in harmful sequelae (although such a reaction is more likely with a wild viral infection than vaccination). *Id.* at 43. Elderly individuals, Dr. Levin maintained, can particularly suffer from the effects of a prolonged cytokine-driven inflammatory response. *Id*. at 53; S. Mohanty et al., *Prolonged Proinflammatory Cytokine Production in Monocytes Modulated by Interleukin 10 After Influenza Vaccination in Older Adults*, 211 J. Infect. Diseases 1174–84 (2015), filed as Ex. 28 (ECF No. 38-1) ("Mohanty").

Mohanty sought to "better understand the effects of aging innate immune responses to the trivalent inactivated influenza vaccine." Mohanty at 1180. To do so, the study considered the *in vivo* immune response, before and after receipt of the flu vaccine, of a 67-patient population—36 of whom were older than 65, while the remainder were between the ages of 21 and 30—looking at levels of different cytokines (pro and anti-inflammatory) and monocytes (white blood cells) before vaccination and then at days two, seven and 28 post-vaccination. *Id.* at 1176, 1180. Mohanty's authors observed an increase in inflammatory monocytes in both age groups in days two to seven, returning to baselines by day 28—thus suggesting that the flu vaccine can have a stimulating impact on the innate immune response. *Id.* at 1180. They also observed a comparable

[6] *See Avila v. Willitis Environmental Remediation Trust*, No. C 99-3941 SI., 2008 WL 360858, at *16 (N.D. Calf. Feb. 6, 2008) (excluding Dr. Levin's opinion because it failed to comply with the reliability standards of *Daubert* and Fed. R. Evid. 702).

increase in cytokine production, although the younger group evidenced a higher level by day 28, and the older studied individuals demonstrated a "delayed increase" at day seven. *Id.* at 1181. In addition, the older studied population showed a "marked age-associated increase" in the production of *anti-inflammatory* cytokines over all time periods, which Mohanty's authors felt contributed to the impaired vaccine response that older individuals often experience (and which vaccine manufacturers have attempted to address through high-dose or adjuvanted vaccines). *Id.* at 1183. Mohanty said nothing about the purported pathologic effects of the flu vaccine in any of the studied populations, and did not observe a chronic increase in the kinds of pro-inflammatory cytokines most associated with post-vaccination malaise.

Vaccines, Dr. Levin maintained, must invoke an inflammatory response if they are to cause later immunity to the pathogen at issue. Tr. at 38–39. In this case, the flu vaccine was the most likely cause of Mr. Martin's condition and death, because of the degree to which it encouraged harmful inflammation. No other pathogen was found, Dr. Levin noted, leaving the vaccine as the "only logical explanation" for what befell Mr. Martin. *Id*. at 36. Dr. Levin also referenced VAERS reports[7] revealing, by his research, nearly 700 instances in which an individual reported pneumonia after the flu vaccine. *Id.* at 85–87; Levin Rep. at 4. He did not, however, substantiate his purported VAERS findings in either of his reports. *See* Levin Supp. Rep. at 3; Tr. at 89–91.

Dr. Levin further proposed that Mr. Martin's susceptibility to an aberrant immune response was evidenced not only by his existing health issues, but by the fact (as Mrs. Martin testified) that in 2013 Mr. Martin appeared to have experienced an aberrant response to a prior flu vaccine (although this conclusion was derived solely from Petitioner's allegations rather than from record evidence). Tr. at 39. In 2015, however, the reaction was worse, given Mr. Martin's age and the extent of his diabetes. *Id.* at 40. Although Dr. Levin seemed to deny that in this case the vaccine's wild virus components "caused" the flu, given their inactivated nature, he did allow for the possibility that "the virus could replicate and cause symptoms," although ultimately he relied on the innate immune reaction leading to a cytokine response as the true driving mechanism herein for the pathologic process that resulted in Mr. Martin's death. *Id.* at 49–50.

On cross examination, Dr. Levin admitted that certain articles he had offered to substantiate his contention that kinds of excessive inflammation could be driven by the immune system rather than directly by infection (via "cytokine storms," for example)[8] said nothing about how a vaccine

[7] VAERS (the Vaccine Adverse Event Reporting System) "accepts and analyzes reports of adverse events (possible side effects) after a person has received a vaccination. Anyone can report an adverse event to VAERS. . . . . VAERS is a passive reporting system, meaning it relies on individuals to send in reports of their experiences to CDC and FDA. VAERS is not designed to determine if a vaccine caused a health problem, but is especially useful for detecting unusual or unexpected patterns of adverse event reporting that might indicate a possible safety problem with a vaccine." *About VAERS*, HHS, https://vaers.hhs.gov/about.html (last visited June 30, 2020).

[8] In partial substantiation for the more general assertion about the harmful impact of excessive cytokine upregulation, Dr. Levin's first report included a citation to a website (www.cytokinestorm.com) that he claimed was probably

could be responsible for such an aberrant process. Tr. at 79–80; J. Bordon et al., *Understanding the Role of Cytokines and Neutrophil Activity and Neutrophil Apoptosis in the Protective Versus Deleterious Inflammatory Response in Pneumonia*, 17 Int'l J. Infect. Diseases 76–83 (2013), filed as Ex. 17 (ECF No. 13-8) ("Bordon"). Thus, while an article like Bordon does discuss the role of "cytokine dysregulation" in the "toxic inflammatory response" brought on by a bacterial pneumonia infection, it does not at all comment on how a vaccine could induce such a pathologic process. Bordon at 81. Dr. Levin also admitted that other than some lab testing suggesting Mr. Martin was experiencing an inflammatory process at the time of death, he could not point to record proof that cytokines generated through an immune response in reaction to vaccination three weeks before were causal in this case, although he favored that conclusion. Tr. at 80–81.

Dr. Levin agreed that support for his contention that cytokine levels could remain high for several weeks post-vaccination was derived from *in vitro* studies involving repeated stimulation with additional doses of vaccine—unlike what Mr. Martin had experienced. Tr. at 81–82; *see also* E. Bernstein et al., *Cytokine Production After Influenza Vaccination in a Healthy Elderly Population*, 16 Vaccine 18:1722-31 (1998), filed as Ex. 19 (ECF No. 13-10) ("Bernstein"). Bernstein tested blood samples from a group of 270 elderly individuals who had received the flu vaccine, and some of its analysis involved a five-day stimulation of those samples with additional amounts of the vaccine. Bernstein at 1724. Bernstein ultimately (and somewhat contrary to Petitioner's causation theory) concluded that the overall elderly response to receipt of the flu vaccine was not sufficiently robust to induce protection against the wild virus—*not* that the flu vaccine had a pathologic impact that could cause persistent cytokine-derived inflammation for days after vaccination. *Id.* at 1730.

Another article only established cytokine elevation peaking within *12 hours* of receipt of the flu vaccine—far shorter a timeframe than the facts of this case. Tr. at 83–84; N. Chatziandreou et a., *Macrophage Death Following Influenza Vaccination Initiates the Inflammatory Response that Promotes Dendritic Cell Function in the Draining Lymph Node*, 18 Cell Reports 2427–40 (2017), filed as Ex. 15 (ECF No. 13-6) ("Chatziandreou"). Chatziandreou's focus was the performance of certain innate immune system-oriented cells called macrophages, and their role helping stimulate post-vaccination inflammation necessary for an adaptive response to a vaccine, but found that increases in relevant pro-inflammatory cytokine levels was far more time-limited than proposed in Petitioner's causation theory. Chatziandreou at 2429–30. And the literature cited in Dr. Levin's report did not directly support his contention that the flu vaccine could instigate a "cytokine storm" sufficient to cause immune system-mediated harm, but instead only explored the harmful nature of a cytokine storm once it comes into being. Tr. at 84–85; J. Boomer et al., *The Changing Immune System in Sepsis*, 5 Virulence 1:45–56 (2014), filed as Ex. 16 (ECF No. 13-7)

created by the National Institutes of Health (Tr. at 101), although the one-page site appears mainly to promote treatments for the condition, and its authors are not disclosed. The website also says nothing about how a vaccine might initiate a cytokine storm.

("Boomer") (discussing the hyper-response of a cytokine storm in reaction to ongoing sepsis, and the causes of immune-suppression that inhibit the immune system under such circumstances).

Besides the causation theory offered, Dr. Levin commented on the pathology evidence. He noted the presence of inflammatory cells (specifically neutrophils) in Mr. Martin's lungs, something that in his view would not have occurred simply due to aspiration of food particles associated with vomiting. Tr. at 47. In Dr. Levin's opinion, these neutrophils evidenced the existence of inflammation in Mr. Martin's respiratory airways that was "pneumonia-like," and would in most circumstances be deemed evidence of an infectious process, but in his view probably the product of an earlier post-vaccination, non-infectious innate response driven by cytokines (produced in turn via an immune response) best characterized as pneumonitis. *Id.* at 47, 68, 92, 93. Otherwise, the pathology findings identified no specific pathogen that might have been causal herein, strengthening in Dr. Levin's view the conclusion that Mr. Martin died from a dysregulated immune process. *Id.* at 48, 52, 53.[9] But the noninfectious inflammation that Dr. Levin posited had occurred could also have made Mr. Martin more susceptible to an infectious process as well. *Id.*

In so maintaining, Dr. Levin discussed whether the autopsy evidence from Mr. Martin's lungs established the existence of an infectious bronchopneumonia (as Respondent's expert Dr. Vargas has proposed—and as Dr. Levin himself had seemed to accept in his report). *See* Levin Rep. at 4 ("the most probable cause of [Mr. Martin's] cardiac arrest was hypoxia associated with his bronchial pneumonia").[10] Dr. Levin maintained, to the contrary, that this diagnostic proposal was made by the pathologist who initially considered Mr. Martin's lung tissue showings without all of the necessary information, including microbiology findings. Tr. at 49. He also disputed that the lung tissue evidence established aspiration pneumonia (in which case Mr. Martin would have developed an infection due to aspiration of food particles after choking), arguing that "it takes days" to develop sufficient inflammatory cells in the lungs to cause that process. *Id.* at 53.

Dr. Levin agreed, however, that the lung tissue slides he reviewed *did* suggest the presence of a bacterial infection, although the failure to identify a pathogen, in his mind, made that less

[9] Respondent pointed out through cross examination, however, that literature Petitioner had filed indicated that a specific pathogen for pneumonia was identified in less than 50 percent of cases. Tr. at 72–73; S. Sethi, *Community-Acquired Pneumonia*, Merck Manuals, https://www.merckmanuals.com/professional/pulmonary-disorders/pneumonia/community-acquired-pneumonia (last visited July 13, 2020), filed as Ex. 18 (ECF No. 13-9) at 1. In response, Dr. Levin tried to maintain that the issue of identification of pathogen was largely dependent on the medical/scientific "sophistication" of the treaters looking for it, although he added he was "not going to argue with somebody who says there was an organism" that here could explain Mr. Martin's diagnosed bronchopneumonia. Tr. at 73.

[10] On cross examination, Respondent questioned Dr. Levin about his review of the pathologic slides prepared from Mr. Martin's lung tissue samples, and the photo he included of one of them in his report. Tr. at 65–69; Levin Rep. at 3. He claimed to agree with the pathology findings in the autopsy (which reasonably can be read to favor bronchopneumonia as an explanatory diagnosis). Tr. at 66.

likely. Tr. at 67–68. He also admitted that the actual autopsy report (Ex. 8) had (and thus contrary to his assertions) *incorporated* the microbiology and other findings that he claimed had not been considered, but still had reached the determination that bronchopneumonia was the correct diagnosis. Ex. 8 at 1; Tr. at 69–70. But Dr. Levin relied on a distinction between "the time the report was issued" and "the time the [diagnostic] decision was made" to defend his claim that the proposed bronchopneumonia diagnosis contained in the pathology report had been arrived at on the basis of incomplete information. Tr. at 70–71.

Dr. Levin also proposed that the overall timeframe of Mr. Martin's alleged illness and then death—with onset of initial symptoms three to five days after vaccination, and death two to three weeks later—was medically acceptable. Tr. at 43. In fact, Dr. Levin seemed to embrace the idea that Mr. Martin developed the pneumonitis that may explain his death "within probably hours" of receipt of the vaccine, despite the lack of record evidence for that specific conclusion, although he later seemed to revert to the concept that onset was actually days later (consistent with Petitioner's testimony). *Id.* at 87, 88. To illustrate grounds for the timeframe aspects of his claim, Dr. Levin used Reye's syndrome (an illness that predominantly affects children)[11] as a comparison, noting that, in reaction to aspirin given to children to fight a viral infection, cytokines released by the liver ultimately impact the brain and cause secondary symptoms not directly attributable to the initial viral infection. Tr. at 44. This kind of immune-mediated process could occur in a timeframe of a few days. *Id.* It would not, however, necessarily *also* be fatal in that same period.

Significantly, Dr. Levin admitted that even though he proposed some kind of aberrant cytokine response, the flu vaccine "was probably a very weak cytokine producer," and hence this (plus Mr. Martin's overall unhealthy condition as well as unique genetic makeup) worked in tandem to draw out the timeframe from initial onset to progression of symptoms and then death two to three weeks later. Tr. at 45–46. He also asserted that Mohanty supported the timeframe at issue, observing that it demonstrated a "sustained innate immune engagement" of up to 28 days after immunization, and that the same persistence was possible with inactivated vaccines like the one Petitioner received. Mohanty at 1181; Tr. at 98–99.

2. <u>Dr. Allan Goldstein</u> – Dr. Goldstein, an internist and pulmonologist, also testified on Petitioner's behalf, and prepared two reports as well. Tr. at 104–61; Report, dated October 30, 2018, filed as Ex. 21 (ECF No. 21-1) ("Goldstein Rep."); Report, dated December 23, 2019, filed as Ex. 39 ("Supp. Goldstein Rep."). He proposed that the flu vaccine caused an inflammatory process that likely created the conditions for a secondary infection in Mr. Martin's lungs, sufficient to produce the bronchopneumonia that led to his death. Tr. at 137–38; Goldstein

[11] Reye's syndrome is "a rare, acute, sometimes fatal disease of childhood, characterized by recurrent vomiting and elevated serum transaminase levels, with distinctive changes in the liver and other viscera; an encephalopathic phase may follow with acute brain swelling, disturbances of consciousness, and seizures. It most often occurs as a sequela of chickenpox or a viral upper respiratory infection." *Dorland's Medical Dictionary Online*, https://www.dorlandsonline.com/dorland/definition?id=111287 (last visited July 1, 2020).

Rep. at 2.

Dr. Goldstein earned his M.D. from Ohio State University in 1965. Goldstein CV, filed on November 15, 2018 as Ex. 22 (ECF No. 12-2), at 1. He is board certified in internal medicine and specializes in pulmonary disease—not infectious disease or pathology. *Id.*; Tr. at 131–32. His practice is currently focused on occupational pulmonary disease. Tr. at 105. Dr. Goldstein also works as an expert in occupational and workers compensations pulmonary disease evaluations, and some litigation where the nature of a person's condition is disputed. *Id*. at 105–06, 127. He has treated patients with lung issues, including pneumonia, in his clinical practice, many of whom were HIV/AIDS patients.[12] *Id.* at 105–06. Besides his clinical practice, Dr. Goldstein was a professor of medicine at Grandview Hospital but stopped teaching eight to nine years ago, and research was never part of his professorial activities. *Id*. at 128–29.

Dr. Goldstein's opinion largely arose from what the medical records revealed about Mr. Martin's health (from the time he received the vaccine until his death), plus some articles provided to him by counsel as well as Petitioner's testimony. Tr. at 133–36. He noted first that Mr. Martin was reported to have had a reaction in 2013 to the flu vaccine (based on Mrs. Martin's testimony), exemplified by flu-like symptoms, and then a similar reaction in February 2015 within three to five days of receipt of the vaccine. *Id.* at 109, 111. This kind of post-vaccination reaction was common, in Dr. Goldstein's experience,[13] although usually unreported since vaccine-induced malaise typically went away. *Id.* at 111–14. Dr. Goldstein did not maintain, however, that this reaction was evidence of a vaccine-caused flu infection, and added that opining on such immunologic topics was outside his area of expertise. Tr. at 143–44.

Thereafter (and through a process that Dr. Goldstein admitted he lacked the expertise to opine upon), some kind of "inflammation related to the vaccine" took hold in Mr. Martin's lung. Tr. at 112, 148. Evidence of the inflammation was provided by the autopsy/pathology report, which revealed neutrophils in his airways and the proposed diagnosis of bronchopneumonia. *Id.* at 110, 112. This bronchopneumonia in turn revealed the existence of a secondary infectious process, likely bacterial in nature, that the record corroborated through evidence such as Mr. Martin's white blood cell count measured at the time of his death. *Id.* at 137, 138. Dr. Goldstein discounted the possibility that the infection was *de novo*, arguing that the "entire clinical picture" relevant to Mr. Martin suggested he was already sick before any bacterial infectious process began, although he could not totally discount the alternative possibility. *Id.* at 139, 155. He differentiated

[12] On cross examination Dr. Goldstein conceded that the HIV/AIDS patients he treated for pneumonia would have been more susceptible to infectious pneumonia "in theory." Tr. at 132.

[13] Dr. Goldstein's second report limits the commonality of this reaction to "elderly or weakened" patients. Supp. Goldstein Rep. at 2; Tr. at 145–46. He also agreed in his testimony that he had witnessed such a reaction in only a handful of patients, none of whom were hospitalized or had developed a secondary pneumonia akin to what is alleged in this case. Tr. at 145–47.

Mr. Martin's earlier symptoms beginning three to five days post-vaccination from what later happened to him, maintaining the earlier symptoms corroborated the secondary character of the bacterial lung infection. *Id.* at 140–41. He acknowledged, however, that all of Mr. Martin's symptoms unfolded within the time of year in which flu and respiratory infections are most common. *Id.* at 141.

The allegedly vaccine-caused inflammation, Dr. Goldstein maintained, likely reduced Mr. Martin's resistance to an infection attributable to bacteria normally present in the lungs but which a person would in most cases naturally resist. Tr. at 112, 113, 159–60. Thus, the bronchopneumonia that may have been observed after Mr. Martin's death (and in fact may have caused it) was likely secondary to vaccine-induced inflammation. *Id.* at 110, 115. Dr. Goldstein did not, however, accept that Mr. Martin might have experienced a noninfectious pneumonitis due to aspiration of food particles, maintaining that a single instance of aspiration from coughing or choking would not be enough to produce the extensive evidence from the pathology slides, and there was not any history of chronic aspiration otherwise. *Id.* at 123–24.

Dr. Goldstein also maintained (although the subject was beyond his expertise) that the flu vaccine could cause the kind of noninfectious pulmonary condition Mr. Martin is alleged to have experienced. He noted that the vaccine's package insert (which does not appear to have been filed in this case) allowed that safety determinations derived from testing trials did not mean that reactions might not still be observed in a clinical practice. Tr. at 107–08. He also proposed that literature established how even an inactivated flu vaccine could increase later susceptibility to a respiratory infection. Tr. at 116–18; B. Cowling et al., *Increased Risk of Noninfluenza Respiratory Virus Infections Associated with Receipt of Inactivated Influenza Vaccine*, 54 Clin. Infect. Diseases 12:1778–83 (2012), filed as Ex. 29 (ECF No. 38-2) ("Cowling").

Cowling was a study involving 115 children (aged six to 15 years) whose health courses were monitored over a nine-month period after receiving the trivalent inactivated flu vaccine, compared to a subsection of that group that had not been vaccinated. Cowling at 1778. The subjects were tested for 19 different non-influenza respiratory viruses (and hence not bacterial-oriented illnesses like pneumonia) in that timeframe. *Id.* at 1778, 1780. Cowling's authors did observe an increased risk of viral respiratory infection thereafter when comparing recipients of the vaccine to an unvaccinated portion of the test group, although the increased risk was most frequently observed in the late winter/early spring of the time period at issue (and thus "after the peak in seasonal influenza activity"). *Id.* at 1780. Cowling's authors opined that the flu vaccine might have reduced the studied sample's "nonspecific immunity" to other kinds of viral infections, and that the duration of this diminished response might persist for two to four weeks post-vaccination, but also that the reliability of their findings was limited by the small sample size and low number of confirmed infections. *Id.* at 1780–81; Tr. at 154.

Other articles, Dr. Goldstein maintained, also established that the flu vaccine could cause or induce an interstitial lung disease. Tr. at 121–22.[14] But, as Respondent pointed out through cross-examination, some such literature was inapposite. Tr. at 150–54. One such article, for example, involved only a single-patient case study, in which an 82-year old man received a dose of the H1N1 flu vaccine, and within two weeks began to experience bloody sputum (distinguishable from Mr. Martin's presentation) that was associated with an acute lung injury. E. Satoh et al., *Acute Lung Injury Accompanying Alveolar Hemorrhage Associated with Flu Vaccination in the Elderly*, 54 Intern. Med. 3193–96 (2015), filed as Ex. 32 (ECF No. 38-5) ("Satoh"), at 3193. The studied individual had suffered a similar injury the year before, however, and also ten days prior to seeking treatment, although he had received an antibiotic as well closer-in-time to the more recent injury. Satoh at 3192–93; Tr. at 150–51.

In another such item, an elderly individual already suffering from chronic obstructive pulmonary disease presented to emergency treaters with fever, malaise, and other symptoms a week before receiving an inactivated flu vaccine. P. Pornsuriyasak et al., *Acute Respiratory Failure Secondary to Eosinophilic Pneumonia Following Influenza Vaccination in an Elderly Man With Chronic Obstructive Pulmonary Disease*, 26 Int'l. J. Infectious Diseases 14–16 (2014), filed as Ex. 33 (ECF No. 38-6) ("Pornsuriyasak"), at 14–15. But the form of pneumonia at issue was eosinophilic[15]—which is distinguishable from bronchopneumonia, and is something Mr. Martin was never proposed to have experienced. Tr. at 152–53. Indeed, Dr. Goldstein admitted that Pornsuriyasak had specifically noted that the flu vaccine was *recommended* for patients susceptible to or suffering from chronic obstructive pulmonary disease. Pornsuriyasak at 14; Tr. at 152–53.

Mr. Martin's history (in particular his diabetes and secondary sequelae) were also likely contributory to a susceptibility to infection after vaccine-induced inflammation. Tr. at 109–10, 114, 119–20. Indeed, his diabetes made him immune-compromised. *Id.* at 156. And rather than the flu vaccine "making its way from the skin through the body into the lungs," Mr. Martin had likely experienced a "general body reaction" to the vaccine. *Id.* at 119. While the reaction took a few days to manifest, Mr. Martin (who is alleged to have hesitated in seeking treatment immediately before his death, due to inclement winter weather) was, in Dr. Goldstein's estimation, like other patients he had seen who had experienced a systemic reaction to a vaccine rather than the vaccine directly attacking the impacted organ. *Id.* at 120. Although such reactions were not common, they could still occur. *Id.* at 120–21.

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[14] Dr. Goldstein additionally maintained he had previously treated patients with an interstitial lung disease, and also asserted that it was more often than not non-infectious in origin. Tr. at 133.

[15] "Eosinophilic pneumonia comprises a group of lung diseases in which eosinophils (a type of white blood cell) appear in increased numbers in the lungs and usually in the bloodstream." Joyce Lee, Eosinophilic Pneumonia, Merck Manuals, https://www.merckmanuals.com/home/lung-and-airway-disorders/interstitial-lung-diseases/eosinophilic-pneumonia (last visited July 13, 2020). Allergic reactions, certain medications, parasites, and fungi are thought to cause eosinophilic pneumonia. *Id.*

At the same time, however, Dr. Goldstein acknowledged that the medical history in this case complicated Petitioner's arguments about the centrality of the flu vaccine in causing Mr. Martin's death. For example, Dr. Goldstein allowed that Mr. Martin's comorbidities might have caused him to suffer a heart attack on February 26, 2015, although he pointed out that the pathology record did not suggest this had occurred. Tr. at 141. In fact, Dr. Goldstein agreed, Mr. Martin had been deemed likely to have experienced a *prior* myocardial infarction, as evidenced by testing after his December 2014 syncopal episode. *Id.* at 142. And if the record better supported the conclusion that Mr. Martin's death was triggered by another such event, then it would be unlikely a flu vaccine administered three weeks before had caused it. *Id.* at 141. Dr. Goldstein also accepted the significance of Mr. Martin's extremely high glucose levels at the time he arrived at the hospital on February 26th, noting that such a reading alone would be grounds for immediate treatment if not full in-patient admission. *Id.* at 158.

Ultimately, Dr. Goldstein opined, the flu vaccine Mr. Martin received was the most likely cause of his subsequent condition and death. But in so opining, he placed considerable weight on the temporal association of vaccination and evidence of Mr. Martin's progressive health deterioration to exclude the possibility of an intercurrent infection (although he also deemed significant the prior report of a reaction in 2013). Tr. at 122–23, 155. Dr. Goldstein also defended the timeframe in which (according to Petitioner) Mr. Martin first began to experience flu-like symptoms three to five days post-vaccination, although he did not question that (as Respondent established in cross-examination) evidence from the Centers for Disease Control ("CDC") supported the conclusion that *any* malaise-like/nonspecific symptoms associated with receipt of the flu vaccine would occur in *less* than twelve hours of vaccination, and subside in two days at most. *Id.* at 149–50; *Influenza Virus*, in Epidemiology and Prevention of Vaccine-Preventable Diseases 187–206 (J. Hamborsky et al., eds., 13th ed. CDC 2015), filed as Ex. Y (ECF No. 26-3) ("Hamborsky"), at 201.

B. *Respondent's Experts*

1. Dr. Sarah Vargas – Dr. Vargas is an anatomic and clinical pathologist, and she prepared two reports and testified on behalf of Respondent. Tr. at 161-283; Report, dated April 12, 2018, filed as Ex. A (ECF No. 15-1) ("First Vargas Rep."); Report, dated February 26, 2019, filed as Ex. X (ECF No. 26-2) ("Second Vargas Rep."). She maintained that Mr. Martin had most likely experienced an infectious pneumonia that was bacterial in origin, that was unrelated to his receipt of the flu vaccine, and that explained his sudden death, given his extensive comorbidities. Tr. at 245–46.

Dr. Vargas is a staff pathologist at Boston Children's Hospital. Tr. at 166. She earned her M.D. from the University of Vermont College of Medicine in 1994. Vargas Updated CV at 2, filed on April 16, 2020 as Ex. BB (ECF No. 41-2). After medical school she completed her residency

in anatomic and clinical pathology at Brigham and Women's Hospital in Boston. *Id.* at 1. Then she completed a pediatric pathology fellowship at Children's Hospital in Boston. *Id.* In her practice she sees mostly children, but also some adults. Tr. at 167. She also performs a few autopsies per weeks and has treated "to many to count" broncho-pneumonia cases over her career. Tr. at 168. Besides her clinical practice she is also an associate professor of pathology at Harvard Medical School. Tr. at 168. While delivering her testimony Dr. Vargas explained that her opinion was mostly from her viewpoint as a pathologist, but also incorporated her clinical experience—which is consistent with the field of pathology. Tr. 254–55.

Dr. Vargas began her testimony by defining acute bronchopneumonia as a "histologic pattern of pneumonia" evident microscopically, and characterized by the presence of a kind of immune inflammatory cell called a neutrophil. Tr. at 174. The neutrophils (most commonly part of the initial/innate immune response in reaction to a bacterial or fungal infection)[16] come from the bloodstream and into the lung's airway lining as well as the air sacs, or alveoli, furthering an inflammatory process. *Id.* at 175–76. For bronchopneumonia, the alveoli near the bronchus, or airway, descending into the lower part of the lung, are most inflamed, making this lung component the "epicenter of the inflammation," but distributing in a patchy manner (meaning only in one lung, or in a scattered manner throughout both). *Id.* at 176 177, 182. Lobar pneumonia, by contrast, features "confluent" neutrophil presence over large and continuous areas of lung, filling all alveoli. *Id.* at 175, 177. Dr. Vargas did not deem it necessary for a person to possess some "predisposing factor" to develop bronchopneumonia, although certain conditions, like diabetes, could make its development more likely. *Id.* at 201–02.

Dr. Vargas opined that Mr. Martin had likely experienced acute bronchopneumonia (although she agreed there was some evidence of confluent inflammation) attributable to some pathogenic organism (more likely bacterial than viral). Tr. at 177, 182. She provided a complete review of the tissue sample slides to support this opinion. *Id.* at 178-84. From such evidence, Dr. Vargas observed an overall patchy distribution of neutrophils consistent with bronchopneumonia. *Id.* at 178–80. Had the infection been viral in nature, there would be evidence of "lymphocytic," or white blood cell-oriented, inflammation, or the effects of viral replication within the cells of the impacted organ (viral inclusion). *Id.* at 183–84. Dr. Vargas saw no such evidence from the slides in question, which she felt strongly supported her conclusion. *Id.* at 184, 201.[17]

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[16] Tr. at 272–73. In so explaining, Dr. Vargas contrasted the "pyogenic" propensity of bacterial or fungal infections – the capacity to elicit inflammatory immune cells like neutrophils—with a viral infection, which she noted did not have this propensity. *Id.* at 181.

[17] Dr. Vargas also took specific issue with the conclusions to be drawn from an image of a lung tissue sample slide that was included in Dr. Levin's first expert report, using his treatment of it to suggest deficiencies in his analysis. Tr. at 161–63; Levin Rep. at 3. As Dr. Vargas explained, the image depicted the lung alveoli, but in her view showed no inflammation. Tr. at 162. Dr. Levin claimed to the contrary, but Dr. Vargas felt he was erroneously pointing out blood vessels in the photo that were "part of the expected anatomy of the lung." *Id.* In addition, arrows on the photo reproduction of the slide pointed, in Dr. Vargas's view, not to eosinophils or inflammation, but rather to white blood

Besides the tissue sample slides, Dr. Vargas maintained that the autopsy/pathology report also supported the post-mortem bronchopneumonia diagnosis.[18] She first noted that the pathologist's summary of findings *began* with bronchopneumonia, highlighting the basis for this conclusion. Tr. at 185, 264–65. In particular, the pathologist had deemed significant the excessive weight of Mr. Martin's right lung—double what would normally have been expected, and also unusually heavier than its left counterpart—and she opined that this was consistent with "a good, well-developed pneumonia," since the lung would have retained more fluid than normal. *Id.* at 186, 187.[19] She agreed that the pathology report did not identify a specific pathogen responsible for Mr. Martin's bronchopneumonia, but felt that the circumstances overall presented "classic" evidence[20] of a bacterial pneumonia, adding that it was common not to be able to identify a pathogen in postmortem testing. *Id.* at 190. In fact, it was common to *discover* pneumonia after death and on autopsy, since it might take some time for the pneumonia to show up early on x-ray (especially given the lack of sensitivity in this particular imaging technique). *Id.* at 196–97.

What was known about Mr. Martin's clinical presentation or lab findings also, in Dr. Vargas's view, supported the bronchopneumonia diagnosis. Bronchopneumonia would usually be characterized by a cough, or shortness of breath, plus a variety of other flu-like symptoms (fever, aches and chills, dizziness, etc.). Tr. at 195–96; Vargas Rep. at 6. Physical collapse without any other presenting symptoms was also "well documented." Tr. at 196. Here, Mr. Martin was noted when brought to the hospital[21] to be displaying abnormal breathing sounds. *Id.* at 196, 199–200; Ex. 7 at 11. His elevated white blood cell count (which evidenced an ongoing inflammatory process) as well as chest x-ray findings were also consistent with the presence of bacterial bronchopneumonia. *Id.* at 196, 244; Ex. 5 at 437; Ex. 7 at 143. Dr. Vargas did not dispute (as

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cells in vessels as would be expected. *Id.* at 163. She also felt this one individual photo did nothing to establish "chronicity of disease," meaning that the inflammatory process long predated Mr. Martin's death. *Id.* at 181. She therefore disputed Dr. Levin's contention that the slide photo in any way supported Petitioner's theory. *Id*.

[18] On cross examination, Dr. Vargas made specific comments about the list of other proposed diagnostic findings after autopsy. Tr. at 264–68. She did not overall express any disagreements with the findings that relate to her opinion. *Id.* at 268–69.

[19] Dr. Vargas did not, however, conclude based on the slides and written pathology findings that Mr. Martin's illness had progressed to acute respiratory distress syndrome, noting that the radiologic evidence did not suggest "whiteout," or shadows covering the images, along with the fact that there was no reported clinical symptoms consistent with severe respiratory failure. Tr. at 187–88. The absence of air in the alveoli (due to the presence of neutrophils) would make them appear "radiopaque," or whiter, on imaging. *Id.* at 199.

[20] Dr. Vargas later emphasized that although it was never "easy" in any case to pinpoint with precision a cause of death based on medical record and pathologic postmortem findings, this case presented based on her experience a "satisfactory and very common explanation." Tr. at 200.

[21] On cross-examination, Dr. Vargas agreed that the record did not suggest Mr. Martin was experiencing bronchopneumonia in December 2014, when he suffered a syncopal episode. Tr. at 229.

stressed by Dr. Levin) that Mr. Martin had also displayed certain inflammation biomarkers (e.g. an elevated sedimentation rate), but deemed them a product of his chronic diabetes and other comorbidities rather than proof of cytokine-driven inflammatory processes due to vaccination. *Id.* at 217–18.

Bronchopneumonia was a “well-known cause of death” generally, Dr. Vargas noted, and in this case Mr. Martin’s comorbidities increased the likelihood that it would have a fatal impact for him. Tr. at 277 (“this was a gentleman who had many chronic diseases that were all things [that] can be fatal or contribute to a terminal fatal event”). Thus, Mr. Martin had “major risk factors” for a heart attack (and had even experienced an undiagnosed myocardial infarction, as evidenced from his December 2014 EKG), along with high blood pressure. *Id*. at 192, 193, 202–03, 232–33, 237. In addition, he had uncontrolled diabetes, which could exacerbate the risk to his heart, would have rendered him immunocompromised, and could also increase the likelihood of a respiratory infection. *Id.* at 193, 230–31, 237, 248–49. Mr. Martin continued in the period post-vaccination to display high blood sugar levels. *Id.* at 240. She admitted, however, that not every one of Mr. Martin’s comorbidities could be deemed contributory, or at least that she had not identified every one as relevant or significant. *See, e.g.*, Tr. at 235–36 (discussing significance of retroperitoneal hematoma observed on autopsy).

Pneumonia would interact with all of the above to the extent it compromised Mr. Martin’s ability to “oxygenate” his blood, thereby depriving the heart of oxygen needed to function and increasing the likelihood of arrhythmia or sudden collapse from heart failure. Tr. at 234–35. The dehydration from diabetes could also impact the blood’s effectiveness. *Id.* at 194; Vargas Rep. at 7. And sepsis (which could cause low blood pressure or impact the heart in other ways) attributable to such a bacterial infection could also result in cardiac arrest. *Id.* at 193–94. The medical record establishes that sepsis was also included at Huntsville Hospital as a potential explanation for Mr. Martin’s death. Ex. 5 at 341; Ex. 7 at 11.

Dr. Vargas could not precisely pinpoint when Mr. Martin’s alleged bronchopneumonia most likely began. She proposed it was likely acute, and that (based on the extent of coverage of neutrophils from review of the lung tissue slides) it might have begun a few days before his death. Tr. at 246, 258. She noted that evidence in support of its likely acute nature was also drawn from the fact that there was no evidence from the tissue sample slides of immune cell “cleanup” of a chronic/preexisting infectious process. *Id.* at 274–75. She also deemed significant reports from the record that in the days immediately preceding Mr. Martin’s collapse and death, he was said not to be feeling well. *Id.* at 278–79, 283. She acknowledged, however, that her report did not address this question in any particularity. *Id.* at 247. She also agreed that a person with some preexisting viral respiratory illness could later “pick up a pneumonia” 17 days after a first infection, but denied that the record in this case demonstrated that this had occurred in Mr. Martin’s case. *Id.* at 255.

Dr. Vargas contested Dr. Levin's conclusion that Mr. Martin's lung condition was attributable to some kind of non-infectious inflammatory process that began in the three weeks before his death. She maintained that the slides and other record evidence clearly demonstrated the existence of neutrophils, which would typically accumulate in response to a bacterial presence in the lung. Tr. at 203, 258–59.[22] She did not read the evidence as suggesting the existence of an interstitial pneumonia—a disease of the lung "interstitium," or fluid-filled support structures in the lungs,[23] as opposed to the air space/bronchi, through which breathed-in air flows. *Id.* at 203–04. She also disputed the possibility that Mr. Martin's pneumonia was chronic or could have existed from the time of his purported onset three to five days post-vaccination, noting that she saw no such evidence from the pathology slides that would support that conclusion, and similarly rejected the concept that it reflected some "superinfection" (meaning a secondary bacterial infection following some prior viral infectious process). *Id.* at 218–19, 251–52, 256.

Dr. Vargas also disagreed with Dr. Levin's argument that the flu vaccine could trigger a process ultimately culminating as a neutrophilic pneumonia akin to what she opined Mr. Martin had experienced, maintaining that his opinion lacked medical or scientific support. Tr. at 205–06; Second Vargas Rep. at 3. She doubted that a plausible mechanism for how this would work could be articulated—especially when, as here, the vaccine had been intradermally administered in an arm rather than directly into the airways. Tr. at 206. Even if a known pathogenic cause of pneumonia, like a bacterium, were to be directly injected into the blood, it would at most cause what she termed a "hematogenous infection" in the lung that would not spread anatomically in the same manner as bronchopneumonia. *Id.* at 206–07. At bottom, Dr. Vargas said she did not "think that a vaccine can make the lungs fill up with neutrophils." *Id.* at 210.[24]

Dr. Goldstein's report and opinion were similarly rejected by Dr. Vargas as unpersuasive and medically unreliable. *Id.* at 207–09. Dr. Vargas took particular issue with Dr. Goldstein's contentions about the nature of the immune response to the flu vaccine, explaining that although vaccines could instigate some "systemic" reaction beyond the situs of administration (i.e., body aches or other more wide-spread symptoms), they did not have a "pathway" to the lung airways sufficient to cause a pneumonia-like reaction. *Id.* at 209–210. She also argued that the literature (primarily case studies) Dr. Goldstein offered to suggest an association between vaccines and certain kinds of pneumonia was distinguishable, mostly because the precise kind of pneumonia at

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[22] Dr. Vargas did admit that there were circumstances where neutrophils might be produced in response to a noninfectious process, but ultimately (and relying on the pathology findings in this case) opined that "it's hard to imagine that it's anything but [in reaction to] bacteria." Tr. at 258, 259–60.

[23] *Dorland's Illustrated Medical Dictionary* 939, 1451 (33d ed. 2020) (hereinafter *Dorland's*).

[24] Dr. Vargas also disputed that there was any evidence that Mr. Martin had experienced an eosinophilic pneumonia (in which clusters of eosinophils, a kind of disease-fighting white blood cell distinct from neutrophils, lead to abscesses in the alveolar spaces), and thus literature offered by Petitioner suggesting vaccines could cause this pneumonia variant did not bear on the case. Tr. at 210–12.

issue did not reflect what Mr. Martin had experienced, or because the illnesses at issue were not bacterial in nature. *Id.* at 212–17.

On cross examination, Dr. Vargas was asked about the evidence (mostly obtained from Petitioner's testimony, but also reflected in contemporaneous records from incidents like the EMT visit) that Mr. Martin had not felt well for some part of the approximately three-week timeframe between vaccination and death. Dr. Vargas acknowledged that it did appear for some of this period that Mr. Martin was "feeling poorly," with a variety of flu-like symptoms (e.g., chills, body ache, GI-related problems). Tr. at 240–41. She also accepted that Mr. Martin had likely begun to feel such symptoms sometime after vaccination, although she contested whether these symptoms were necessarily indicative of the acute respiratory pneumonia that was observed in his autopsy, reflective alone of a respiratory infection, or began as early as Petitioner has alleged. *Id.* at 250–51, 253, 271–72. She did, however, agree that a 17-day time course was consistent with a "superinfection," although she reiterated that she saw no evidence from the pathology report and slides that Mr. Martin had experienced a chronic infectious process of any kind before his pneumonia likely began. *Id.* at 252.

2. <u>Dr. Kathleen Collins</u> – Dr. Collins, an infectious disease and immunology expert, also testified for Respondent in support of the expert reports she prepared. Tr. at 284–411; Report, dated April 13, 2018, filed as Ex. I (ECF No. 16-1) ("Collins Rep."); Report, dated February 20, 2019, filed as Ex. W (ECF No. 26-1) ("Supp. Collins Rep."). She opined that Mr. Martin's death was attributable to his comorbidities coupled with a likely bacterial-in-origin bronchopneumonia, rather than to the flu vaccine. Tr. at 308, 380.

Dr. Collins specializes in microbiology, immunology, and infectious disease—she is board certified in infectious disease but she is not a per se immunologist. Tr. at 287–88, 293. She earned her M.D. and Ph.D. in molecular biology and genetics from Johns Hopkins School of Medicine in 1993; Tr. at 285. Subsequently, Dr. Collins served as a postdoctoral fellow in Dr. David Baltimore's[25] laboratory at MIT from 1996 to 1998. Collins Updated CV at 1, filed on January 29, 2020 as Ex. CC (ECF No. 41-3); Tr. at 286. There she conducted research on "understanding the cell-mediated immune response to viral infections. Tr. at 286. Dr. Collins currently teaches immunology and virology at the University of Michigan. *Id*. at 287–88. She sees patients (among whom are pneumonia patients) for about four weeks out of the year total, although this time is often broken up into shorter periods. *Id*. at 288, 363. Dr. Collins also works with the National Institutes of Health on vaccine development. *Id*. at 292–93.

From the filed record, Dr. Collins made several observations bearing on her ultimate

[25] Dr. David Baltimore is an American Biologist and 1975 Nobel laureate for his work in virology. David Baltimore, The Nobel Prize, https://www.nobelprize.org/prizes/medicine/1975/baltimore/biographical/ (last visited July 7, 2020); *see also* Tr. at 286.

opinion. Although Petitioner asserts that Mr. Martin's prior exposure to the flu vaccine resulted in a reaction, Dr. Collins observed no evidence of an allergic response that would have suggested to treaters that he should not receive it in the future. Tr. at 294–95. Indeed, the vaccine was not specifically contraindicated for him by treaters, and the records revealed Mr. Martin had positively answered treater questions about his ability to tolerate it. *Id.* at 295. In Dr. Collins's view, the flu vaccine was particularly appropriate for a diabetic person like Mr. Martin, who was likely not to respond well to wild viral infections. *Id.* at 296.

Dr. Collins then went on to evaluate Mr. Martin's overall medical history in 2014 and 2015. He consistently displayed high blood sugar levels, establishing that his diabetes was uncontrolled. Tr. at 299–300. Dr. Collins highlighted the different complications from his diabetes, including his 2014 foot infection—a common presentation of diabetes, and revealing poor circulation coupled with a dysfunctional immune response. *Id*. at 298. The antibiotics he took for the infection resulted in a renal failure complication that same year. *Id.* Then, toward the end of 2014, Mr. Martin had some syncopal events, and in the medical work-up that followed his undiagnosed heart attack was revealed. *Id.* at 299. The records in Dr. Collins's reading suggested treaters felt his syncope could be a product of diabetes-associated dehydration (which resulted in abnormally low blood pressure). *Id.* at 300–01. Efforts to better explain the constellation of symptoms that Mr. Martin displayed were cut short by his death. *Id.* at 301–02.

Dr. Collins next pointed out the record from Mr. Martin's VA telehealth visit with a nurse on February 24, 2015. Tr. at 302–03; Ex. 5 at 101–10. Although Petitioner has alleged that by this time Mr. Martin felt sick and had desired more direct medical intervention, the notes from the telehealth meeting only recorded that he was experiencing lower back and hip pain (which Dr. Collins understood from the record to be a chronic concern), and also (based on a checklist) ran down a number of other symptoms and conditions. Tr. at 302–43. Dr. Collins felt the record should have revealed some instances of complaints of the flu-like symptoms if in fact Mr. Martin had been experiencing them at the time. *Id.* at 303.

The other records from the day of Mr. Martin's death were, in Dr. Collins's reading, consistent with Petitioner's assertions about the immediate circumstances of the morning of February 26, 2015. Tr. at 304. Thus, Mr. Martin had been "sick with a cold" a few days prior to his collapse, although immediate ER tests established an exceedingly high blood sugar reading. *Id.* at 305. Dr. Collins opined this finding was relevant to Mr. Martin's heart stopping, as it was further proof of the intensity of his diabetes and the impact it would have had on his blood pressure and circulation. *Id.* at 306. The pathology evidence about fluid and lung congestion due to neutrophils further suggested the impact on oxygenation of the blood, which would in her view also have affected his heart function. *Id.* The lung findings as of this point were also different from x-rays taken at the time of Mr. Martin's syncopal event in December 2014, further highlighting the greater risk Mr. Martin faced at the time of his death. *Id.* at 307.

Based upon the above, Dr. Collins maintained it was likely that Mr. Martin's death was attributable to a "community-acquired pneumonia." Tr. at 308; Collins Rep. at 4. She felt the record evidence, supplied by Petitioner's contemporaneous statements to treaters, that Mr. Martin had been sick for a few days before "would go along with a pneumonia." Tr. at 309–10. The pathology report (as explained by Dr. Vargas) was also strongly consistent with this conclusion, as was lab work performed at his arrival to the hospital suggesting a high white blood cell count (and thus the existence of an infectious process at work). *Id.* at 309, 312. And emergency treaters used an antibiotic, suggesting they too suspected a bacterial infectious process. *Id.* at 315–16; Ex. 7 at 119. Dr. Collins did not, however, deem the claimed symptoms that began closer in time to vaccination as likely related, since they seemed more consistent with a GI-tract-oriented disease, and did not describe respiratory symptoms (e.g., cough, shortness of breath, best pain, phlegm production). Tr. at 311–12.

Dr. Collins strongly disputed Petitioner's assertion that Mr. Martin's death was associated with his receipt of the flu vaccine. She noted as a threshold matter that a person could develop bronchopneumonia without first receiving the flu vaccine. Tr. at 314. In fact, the bacterial infectious process necessary to result in bronchopneumonia did not require a preexisting risk factor, and could thus affect a totally healthy person. *Id.* No treaters from the filed medical record seem to have proposed the flu vaccine could have caused Mr. Martin's death, and Dr. Collins added that she would herself not have considered it as a possible pathologic factor. *Id.* at 316–17. In addition, Dr. Collins opined that the February 5th vaccination was too remote in time to Mr. Martin's collapse and death to be causal. Tr. at 318. Rather, the record suggested he experienced acute symptoms immediately around the February 26th event, with a "well-documented history" that up until right before that day he was in usual health. *Id.*

More broadly, Dr. Collins disputed the contention that the flu vaccine has ever been reliably associated with any form of pneumonia, or true flu-like symptoms. Tr. at 330–34, 335–37. In so maintaining, she noted that the version of the vaccine Mr. Martin had received was inactivated, meaning its viral components could not reproduce within a cell akin to a wild virus and cause the kind of symptoms that a wild infection would inherently provoke. *Id.* at 335. She also questioned whether literature offered on this point in fact squarely supported Petitioner's argument. *Id.* at 330–31. Chatziandreou, for example, was an animal study that said nothing about any association between the flu vaccine and respiratory diseases like pneumonia. *Id.* at 331.

Dr. Collins similarly discounted other categories of evidence relied upon by Petitioner's experts as corroborative of causation. VAERS reports of pneumonia following receipt of the flu vaccine, for example, only establish a temporal association between vaccine and illness, are not consistently reported, lack scientific controls that would permit conclusions to be drawn about a causal association, and can also fail to take into account confounding factors. Tr. at 331–33.

Similarly, the fact that no other possible pathogen was identified to explain Mr. Martin's purported infection was not meaningful in Dr. Collins's experience—and therefore did not leave the vaccine as the most likely explanation. *Id.* at 334–35. She denied as well that a vaccine could elicit neutrophils in the lungs—adding her view that if the vaccine could damage the lungs in *any* way, there would exist substantially more evidence of this occurring. *Id.* at 343, 345–46.

Besides offering a direct opinion, Dr. Collins commented on aspects of the opinions offered by Petitioner's experts. As Dr. Collins explained, the immune system's usual regulation of cytokine secretion could sometimes fail (often as a result of an existing infection or some other cause for an abnormal immune activation), resulting in overproduction of such immune cells, in the form of a cytokine storm, and thereby causing systemic harm. Tr. at 319–20. She cited sepsis (a bacterial infection leading to systemic inflammation throughout the body) as the kind of accepted medical trigger for a cytokine storm. *Id.* at 320–21. But Dr. Levin's arguments about the propensity of vaccines to cause inflammatory "cytokine storm" cascades were undercut by findings of the Institute of Medicine. Collins Rep. at 6; Tr. at 318–19; Institute of Medicine, *Adverse Effects of Vaccines: Evidence and Causality* 76 (Kathleen Stratton et al., 2012), filed as Ex. V on Apr. 16, 2018 (ECF No. 17-4) (admitting that "more subtle imbalances" of cytokines may occur after administration of vaccines other than flu vaccine, but concluding that "no evidence that directly or indirectly supports the oversecretion of cytokines as an operative mechanism was found"). Dr. Collins was otherwise aware of no reliable medical or scientific literature establishing that vaccination could cause a cytokine storm, or even play a role in the breakdown of immune regulatory function necessary to result in it. Tr. at 320. And the record in this case did not support the conclusion that Mr. Martin himself had experienced such an uncontrolled immune reaction (at least in response to the flu vaccine three weeks prior to his death). *Id.* at 321–22.[26] His preexisting diabetes did not suggest a propensity for an overactive immune response (and if anything, suggested a *slower*, less robust response). *Id.* at 323–24.

Dr. Collins similarly found unpersuasive Dr. Levin's contentions that Mr. Martin had likely experienced an upregulation of cytokines after vaccination, and that such excessive cytokine levels could thereafter last several weeks. She saw no such evidence of cytokine elevation in the actual medical record. *Id.* at 324, 321. Dr. Collins also observed that the literature offered in support of this contention, like Bernstein, only established that a person who had previously received the flu vaccine (and thus was primed to respond to its antigens) could generate an immune response if re-exposed—*not* that the second response would be reflected in "continuously elevated" levels of cytokines. *Id.* at 325. On the contrary—the cytokines responsive to vaccination due to adaptive immune "memory" of an earlier flu vaccine's receipt would generally peak rapidly in any event, and the overall robustness of immune response to receipt of the vaccine was ultimately lower in

[26] For the same reasons, Dr. Collins rejected the proposal in Dr. Levin's first report that Mr. Martin experienced "hypercytokinemia," noting in particular that even a vaccine reaction that was documented would usually be localized to the site of vaccination, and not focused on an inflammatory process in the lungs. Tr. at 322–23.

elderly populations. Tr. at 326; Bernstein at 1730.[27]

Mohanty (the article filed by Petitioner but only addressed by Dr. Levin at hearing rather than in his reports) did not, in Dr. Collins's reading, support the contention that certain individuals (the elderly or immune-compromised) would likely experience a temporally-prolonged cytokine elevation period after vaccination. Tr. at 337–40. Dr. Collins agreed that older individuals would mount a less-robust immune challenge to pathogen, and that the overall process of cytokine regulation in response might take longer. *Id.* at 337–38. However, she noted that not all cytokines perform the same task, and there are both pro and anti-inflammatory cytokines that are produced as part of the immune system's self-regulation. *Id.* at 338–39. Mohanty only established an overall course for production of *different* types of cytokines—not that the allegedly-pathogenic effect of initially-produced proinflammatory cytokines would inherently persist, and cause symptoms, in the timeframe alleged by Dr. Levin. *Id.* at 339.[28] Dr. Collins also noted that Mr. Martin was not in the same age cohort as the older studied population in Mohanty, and that the article said nothing at all about how a vaccine-induced inflammatory response beginning in the blood would migrate to the lungs. *Id.* at 340.[29]

Dr. Collins similarly disputed many of Dr. Goldstein's expert contentions. She concurred with Dr. Vargas (and her specific citation to CDC publications) that post-vaccination malaise could occur, and have a flu-like appearance, but maintained that it would be short-lived. Tr. at 344–45, 398–99. She argued that certain literature Dr. Goldstein had more recently offered only suggested that transient, cytokine-associated malaise could occur in such a brief time period—not that a pathogenic response was likely on a longer timeframe akin to what is alleged to have occurred in this case. *Id.* at 347–49; L. Christian et al., *Proinflammatory Cytokine Responses Correspond with Subjective Side Effects After Influenza Virus Vaccination*, 33 Vaccine 29:3360-66 (2015), filed as Ex. 30 (ECF No. 38-3) ("Christian"). Christian was in fact mostly concerned with evaluating (in a population of women only) the relationship between immediate, subjective post-vaccination

[27] In so asserting, Dr. Collins noted that other literature offered by Dr. Levin to support his contention actually underscored the rapidity of the post-vaccination cytokine peak, rather than suggested that elevated cytokine levels would last for a long period after vaccination. Tr. at 327–30; *see, e.g.*, K. Talaat et al., *Rapid Changes in Serum Cytokines and Chemokines in Response to Inactivated Influenza Vaccination,* 12 Influenza Other Resp. Viruses 202–10 (2018), filed as Ex. 24 (ECF No. 21-4), at 202 (cytokine levels in response to receipt of trivalent inactivated flu vaccine administered to 20 subjects peaked in 24 hours of vaccination, with no measured cytokine sustaining in elevated levels for more than two weeks).

[28] In fact (as Dr. Collins observed), Mohanty found that vaccines likely were *less* effective for older adults because of a failure in their immune systems to regulate the overall immune response (here, through the production of anti-inflammatory cytokines)—*not* that vaccines were themselves more pathogenic. Tr. at 340; Mohanty at 1183.

[29] Dr. Collins expanded on this point when asked about assertions Dr. Vargas made about the low likelihood that an intradermally-administered vaccine would impact the respiratory system. Tr. at 341–43. An infectious process that began through the blood would not, in Dr. Collins's experience, appear on X-ray or other imaging the same as one (like here) that was clearly impacting the respiratory pathways. *Id.* at 343.

complaints, like soreness at the site of administration, and subsequent inflammatory responses (which would point to the vaccine's effectiveness). Christian at 3366 (p. 9 of ECF No. 38-3). Dr. Collins agreed that articles like Cowling did reliably observe an increased risk of *viral* (non-flu) respiratory infections in children after receipt of the flu vaccine, but noted that its findings had not since been updated, it offered no mechanistic explanation for causation, and it otherwise did not offer a good comparison to Mr. Martin's likely bacterial infection-caused bronchopneumonia. Tr. at 349–51. And she disputed the evidentiary value of case reports offered by Dr. Goldstein to establish causal association. Tr. at 353–54.

On cross-examination, Dr. Collins was questioned about the extent to which her first written report concluded (consistent with Dr. Levin's opinion) that in fact Mr. Martin had experienced a noninfectious pneumonitis (rather than bacterial bronchopneumonia), pointing out language in her report supportive of that view. Tr. at 365–70; Collins Rep. at 4, 7. Dr. Collins agreed that record evidence (in particular evidence of vomit in Mr. Martin's mouth at the time EMTs attempted resuscitation) did suggest the presence of "[c]hemical pneumonitis from acid aspiration." Tr. at 367; Collins Rep. at 7. She also admitted concluding that such a noninfectious pneumonitis could have contributed to the events culminating in his death. Tr. at 381. However, Dr. Collins (both in her report and testimony) also allowed for the possibility that Mr. Martin has experienced "community-acquired pneumonia" of a bacterial origin, and ultimately deferred to Dr. Vargas on the issue. Collins Rep. at 7; Tr. at 368–71. Her second report more clearly incorporated Dr. Vargas's opinion (presumably because both of Respondent's experts' first reports were prepared and filed simultaneously),[30] and clearly included the opinion that Mr. Martin's respiratory condition was in part the result of a bacterial infection, in addition to her prior discussion of the possibility it was noninfectious. Supp. Collins Rep. at 4–5.

Dr. Collins also was asked about the timeframe in which Mr. Martin's pneumonia developed, and what that said about its likely etiology. She agreed that a noninfectious pneumonitis could occur faster than a bacterial infectious process, but denied that the approximately 15 days from the time Mr. Martin first seemed to complain of flu-like symptoms to the date of his death was a reasonable temporal course for development of a bacterial pneumonia. Tr. at 376–78. She also emphasized that Mr. Martin's history revealed that his numerous risk factors (which long predated vaccination) were nonspecific for a respiratory condition—but the same was true of the symptoms that Petitioner alleges he began experiencing three to five days post-vaccination, which were somewhat consistent with his health before vaccination, or reflective of a GI-oriented condition distinguishable from a respiratory illness like pneumonia. *Id.* at 382–84, 387–88.

Dr. Collins added that she had heard and accepted Petitioner's allegations about Mr. Martin's post-vaccination malaise and flu-like symptoms, but ultimately felt it most likely that (a) the symptoms Petitioner alleged to have observed in her husband were not related to the

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[30] *See* ECF Nos. 15-1 (Vargas Rep.) and 16-1 (Collins Rep.), dated April 12, 2018, and April 13, 2018, respectively).

bronchopneumonia seen from the pathology evidence, and (b) Mr. Martin's bronchopneumonia likely began closer in time to his death, rather than three to five-days post-vaccination. Tr. at 383, 387–89. In so opining, Dr. Collins gave some weight to the fact that Mr. Martin did not appear to have complained of illness or malaise-like symptoms during his February 24th telehealth visit, along with the fact that Petitioner made contemporaneous statements to first responders on the 26th that Mr. Martin had only felt unwell for a few days or a week prior to his death. *Id.* at 389–90. She did agree, however, that the record from when Mr. Martin was taken to the ER mentioned he had been "sick with [a] cold for *days*" (thus allowing for the possibility that the period of time might have exceeded a week, given the indeterminate nature of "days"). *Id.* at 391–93; Ex. 7 at 104 (emphasis added).

C. *Fact Witnesses*

The sole fact witness to testify in this matter was Petitioner herself. Tr. at 4–32. Her testimony was consistent with the witness statements filed in this case, although she provided some additional details about the circumstances of her husband's health in February 2015.

Petitioner recalled that Mr. Martin received vaccines "very rarely," and that he had been administered the flu vaccine on February 5, 2015 (a Thursday) at his doctor's recommendation, due to his ongoing diabetes. Tr. at 10, 11–12. (He had also received the vaccine in 2013, and had (in Petitioner's uncorroborated recollection) subsequently experienced flu-like symptoms for two weeks after. *Id.* at 11). The evening after receiving the vaccine in February 2015, Mr. Martin seemed fine, and into that weekend as well, with Petitioner only noticing that her husband was not feeling well by Monday, February 9, 2015. *Id.* at 13–14.

The rest of that week and into the next, Petitioner testified, Mr. Martin continued to feel sick, with body aches, nausea, and other progressively worse symptoms, that made it impossible for him to go out to dinner or socialize. Tr. at 14–15. Eventually, Mr. Martin phoned a VA doctor on February 19, 2015, to seek advice on his condition, although there is no filed record of this call. *Id.* at 16, 25. He thereafter continued to feel unwell, and had planned to seek in-person treatment but was unable to do so because of a snowstorm experienced in Huntsville right around the date of his death. *Id.* at 17–18. Petitioner did acknowledge Mr. Martin's telehealth call on February 24, 2015, but suggested that call was limited to discussion of his breathing and diabetes control issues, and thus was not sure if it presented an occasion for him also to mention his alleged other symptoms. *Id.* at 29.

On the evening of February 25, 2015, Mrs. Martin and her husband fell asleep in their home game room while watching some movies. Tr. at 18. Early the next morning, Petitioner recalled, Mr. Martin awoke and informed her he felt dizzy, then went to the bathroom. *Id.* at 18–19. After five minutes or so, Mrs. Martin went to check on him (having heard no noises coming from the

bathroom), and found her husband slumped over the toilet, unresponsive. *Id.* at 19. She immediately called 911 and attempted to perform CPR. *Id.* at 19, 20. In the process of so doing, she observed vomit in and around his mouth, which she attempted to clean. *Id.* at 20–21.[31] She informed the arriving paramedics that Mr. Martin had been sick recently (and in her mind since a few days after receiving the flu vaccine twenty days before). *Id.* at 21, 22. She thereafter travelled to the hospital with the paramedics. *Id.* at 22.

Mrs. Martin acknowledged her husband's pre-existing diabetes, which she recalled had been diagnosed in 2001. Tr. at 7–8. He took medications for it, although she could not recall the various complications and sequelae that the record establishes Mr. Martin suffered from in connection with his diabetes. *Id.* at 8. In fact, Petitioner maintained that Mr. Martin was "in good health" prior to his vaccination, and that he attended to his health and sought medical treatment in a seasonable manner when appropriate. *Id.* at 8–9. At most, Petitioner admitted that Mr. Martin struggled to keep his blood sugar levels in control. *Id.* She did also acknowledge, however, Mr. Martin's fainting in late 2014, although she suggested it was a single occurrence. *Id.* at 9–10.

III. Procedural History

As stated above, this case was initiated in February 2017. The filing of records was completed that June, and Respondent's Rule 4(c) Report opposing an entitlement award was filed in August 2017. ECF No. 10. Thereafter, and until the winter of 2019, the parties engaged the experts whose opinions are discussed above and filed reports from each. In February 2019, I set this matter for hearing in February 2020, and the hearing went forward as planned. The parties opted not to file post-hearing briefs, and the matter is now fully ripe for adjudication.

IV. Applicable Law

A. *Petitioner's Overall Burden in Vaccine Program Cases*

To receive compensation in the Vaccine Program, a petitioner must prove either: (1) that he suffered a "Table Injury"—i.e., an injury falling within the Vaccine Injury Table—corresponding to one of the vaccinations in question within a statutorily prescribed period of time or, in the alternative, (2) that his illnesses were actually caused by a vaccine (a "Non-Table Injury"). *See* Sections 13(a)(1)(A), 11(c)(1), and 14(a), as amended by 42 C.F.R. § 100.3; § 11(c)(1)(C)(ii)(I); *see also Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321 (Fed.

[31] This allegation is also not corroborated by the medical record and was not addressed in her prehearing statements, although Petitioner maintained merely that she was not asked to do so. Tr. at 30.

Cir. 2010); *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006).[32] In this case, Petitioner does not assert a Table claim.

For both Table and Non-Table claims, Vaccine Program petitioners bear a "preponderance of the evidence" burden of proof. Section 13(1)(a). That is, a petitioner must offer evidence that leads the "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." *Moberly*, 592 F.3d at 1322 n.2; *see also Snowbank Enter. v. United States*, 6 Cl. Ct. 476, 486 (1984) (mere conjecture or speculation is insufficient under a preponderance standard). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Human Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, a petitioner must demonstrate that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352–53 (Fed. Cir. 1999)); *Pafford v. Sec'y of Health & Human Servs*., 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner may not receive a Vaccine Program award based solely on his assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. Section 13(a)(1).

In attempting to establish entitlement to a Vaccine Program award of compensation for a Non-Table claim, a petitioner must satisfy all three of the elements established by the Federal Circuit in *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (2005): "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury."

Each of the *Althen* prongs requires a different showing. Under *Althen* prong one, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355–56 (citations omitted). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Such a theory must only be "legally probable, not medically or scientifically certain." *Id.* at 549.

Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378–79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F.3d at 1325–26). Special masters, despite their expertise, are not

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[32] Decisions of special masters (some of which I reference in this ruling) constitute persuasive but not binding authority. *Hanlon v. Sec'y of Health & Human Servs.*, 40 Fed. Cl. 625, 630 (1998). By contrast, Federal Circuit rulings concerning legal issues are binding on special masters. *Guillory v. Sec'y of Health & Human Servs.*, 59 Fed. Cl. 121, 124 (2003), *aff'd* 104 F. Appx. 712 (Fed. Cir. 2004); *see also Spooner v. Sec'y of Health & Human Servs.*, No. 13-159V, 2014 WL 504728, at *7 n.12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014).

empowered by statute to conclusively resolve what are essentially thorny scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury.

In discussing the evidentiary standard applicable to the first *Althen* prong, the Federal Circuit has consistently rejected the contention that it can be satisfied merely by establishing the proposed causal theory's scientific or medical *plausibility*. *See Boatmon v. Sec'y of Health & Human Servs.*, 941 F.3d 1351, 1359 (Fed. Cir. 2019); *see also LaLonde v. Sec'y of Health & Human Servs.*, 746 F.3d 1334, 1339 (Fed. Cir. 2014) ("[h]owever, in the past we have made clear that simply identifying a 'plausible' theory of causation is insufficient for a petitioner to meet her burden of proof." (citing *Moberly*, 592 F.3d at 1322)). Petitioners otherwise always have the ultimate burden of establishing their *overall* Vaccine Act claim with preponderant evidence, regardless of what evidentiary level of evidence on the "can cause" prong is required. *W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citations omitted); *Tarsell*, 133 Fed. Cl. at 793 (noting that *Moberly* "addresses the petitioner's overall burden of proving causation-in-fact under the Vaccine Act" by a preponderance standard).

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375–77; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). In establishing that a vaccine "did cause" injury, the opinions and views of the injured party's treating physicians are entitled to some weight. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as particularly trustworthy evidence, since they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

Medical records and statements of a treating physician, however, do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs*., 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct - that it must be accepted in its entirety and cannot be rebutted"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should be weighed against other, contrary

evidence also present in the record—including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 742, 749 (2011) (not arbitrary or capricious for special master to weigh competing treating physicians' conclusions against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Veryzer v. Sec'y of Dept. of Health & Human Servs.*, No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review denied*, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 F. Appx. 765 (Fed. Cir. 2012).

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must align with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. denied after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 503 F. Appx. 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for rev. denied* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

B. *Legal Standards Governing Factual Determinations*

The process for making determinations in Vaccine Program cases regarding factual issues begins with consideration of the medical records. Section 11(c)(2). The special master is required to consider "all [] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as the "results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." Section 13(b)(1)(A). The special master is then required to weigh the evidence presented, including contemporaneous medical records and testimony. *See Burns v. Sec'y of Health & Human Servs*., 3 F.3d 415, 417 (Fed. Cir. 1993) (it is within the special master's discretion to determine whether to afford greater weight to contemporaneous medical records than to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such determination is evidenced by a rational determination).

Medical records that are created contemporaneously with the events they describe are presumed to be accurate and "complete" (i.e., presenting all relevant information on a patient's health problems). *Cucuras*, 993 F.2d at 1528; *Doe/70 v. Sec'y of Health & Human Servs.*, 95 Fed. Cl. 598, 608 (2010) ("[g]iven the inconsistencies between petitioner's testimony and his contemporaneous medical records, the special master's decision to rely on petitioner's medical

records was rational and consistent with applicable law"), *aff'd sub nom. Rickett v. Sec'y of Health & Human Servs*., 468 F. Appx. 952 (Fed. Cir. 2011) (non-precedential opinion). This presumption is based on the linked propositions that (i) sick people visit medical professionals; (ii) sick people honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Human Servs.*, No. 11-685V, 2013 WL 1880825, at *2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013); *Cucuras v. Sec'y of Health & Human Servs.*, 26 Cl. Ct. 537, 543 (1992), *aff'd*, 993 F.2d at 1525 (Fed. Cir. 1993) ("[i]t strains reason to conclude that petitioners would fail to accurately report the onset of their daughter's symptoms").

Accordingly, if the medical records are clear, consistent, and complete, then they should be afforded substantial weight. *Lowrie v. Sec'y of Health & Human Servs.*, No. 03-1585V, 2005 WL 6117475, at *20 (Fed. Cl. Spec. Mstr. Dec. 12, 2005). Indeed, contemporaneous medical records are generally found to be deserving of greater evidentiary weight than oral testimony—especially where such testimony conflicts with the record evidence. *Cucuras*, 993 F.2d at 1528; *see also Murphy v. Sec'y of Dep't of Health & Human Servs.*, 23 Cl. Ct. 726, 733 (1991) (citing *United States v. United States Gypsum Co.*, 333 U.S. 364, 396 (1947) ("[i]t has generally been held that oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight.")).

There are, however, situations in which compelling oral testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. *Campbell v. Sec'y of Health & Human Servs*., 69 Fed. Cl. 775, 779 (2006) ("like any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking"); *Lowrie*, 2005 WL 6117475, at *19 ("'[w]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent'") (quoting *Murphy*, 23 Cl. Ct. at 733)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. *Andreu*, 569 F.3d at 1379; *Bradley v. Sec'y of Health & Human Servs*., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

When witness testimony is offered to overcome the presumption of accuracy afforded to contemporaneous medical records, such testimony must be "consistent, clear, cogent, and compelling." *Sanchez*, 2013 WL 1880825, at *3 (citing *Blutstein v. Sec'y of Health & Human Servs*., No. 90-2808V, 1998 WL 408611, at *5 (Fed. Cl. Spec. Mstr. June 30, 1998)). In determining the accuracy and completeness of medical records, the Court of Federal Claims has listed four possible explanations for inconsistencies between contemporaneously created medical records and later testimony: (1) a person's failure to recount to the medical professional everything that happened during the relevant time period; (2) the medical professional's failure to document

everything reported to her or him; (3) a person's faulty recollection of the events when presenting testimony; or (4) a person's purposeful recounting of symptoms that did not exist. *Lalonde v. Sec'y of Health & Human Servs*., 110 Fed. Cl. 184, 203-04 (2013), *aff'd*, 746 F.3d 1334 (Fed. Cir. 2014). In making a determination regarding whether to afford greater weight to contemporaneous medical records or other evidence, such as testimony at hearing, there must be evidence that this decision was the result of a rational determination. *Burns*, 3 F.3d at 417.

C. *Analysis of Expert Testimony*

Establishing a sound and reliable medical theory often requires a petitioner to present expert testimony in support of his claim. *Lampe v. Sec'y of Health & Human Servs*., 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 594–96 (1993). *See Cedillo v. Sec'y of Health & Human Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (citing *Terran v. Sec'y of Health & Human Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999)). "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592–95).

The *Daubert* factors play a slightly different role in Vaccine Program cases than they do when applied in other federal judicial fora (such as the district courts). *Daubert* factors are usually employed by judges (in the performance of their evidentiary gatekeeper roles) to exclude evidence that is unreliable and/or could confuse a jury. In Vaccine Program cases, by contrast, these factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs*., 94 Fed. Cl. 53, 66–67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). The flexible use of the *Daubert* factors to evaluate the persuasiveness and reliability of expert testimony has routinely been upheld. *See, e.g.*, *Snyder*, 88 Fed. Cl. at 742–45. In this matter (as in numerous other Vaccine Program cases), *Daubert* has not been employed at the threshold, to determine what evidence should be admitted, but instead to determine whether expert testimony offered is reliable and/or persuasive.

Respondent frequently offers one or more experts of his own in order to rebut a petitioner's case. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion

"connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)); *see also Isaac v. Sec'y of Health & Human Servs*., No. 08-601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for rev. denied*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 F. Appx. 999 (Fed. Cir. 2013) (citing *Cedillo*, 617 F.3d at 1339). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325–26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs*., 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

Expert opinions based on unsupported facts may be given relatively little weight. *See Dobrydnev v. Sec'y of Health & Human Servs.*, 556 F. App'x. 976, 992–93 (Fed. Cir. 2014) ("[a] doctor's conclusion is only as good as the facts upon which it is based") (citing *Brooke Group Ltd. v. Brown & Williamson Tobacco Corp.*, 509 U.S. 209, 242 (1993) ("[w]hen an expert assumes facts that are not supported by a preponderance of the evidence, a finder of fact may properly reject the expert's opinion")). Expert opinions that fail to address or are at odds with contemporaneous medical records may therefore be less persuasive than those which correspond to such records. *See Gerami v. Sec'y of Health & Human Servs.*, No. 12-442V, 2013 WL 5998109, at *4 (Fed. Cl. Spec. Mstr. Oct. 11, 2013), *aff'd*, 127 Fed. Cl. 299 (2014).

D. *Consideration of Medical Literature*

Both parties filed medical and scientific literature in this case, but not every filed item factors into the outcome of this decision. While I have reviewed all the medical literature submitted in this case, I discuss only those articles that are most relevant to my determination and/or are central to Petitioner's case—just as I have not exhaustively discussed every individual medical record filed. *Moriarty v. Sec'y of Health & Human Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("[w]e generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision") (citation omitted); *see also Paterek v. Sec'y of Health & Human Servs.,* 527 F. Appx. 875, 884 (Fed. Cir. 2013) ("[f]inding certain information not relevant does not lead to—and likely undermines—the conclusion that it was not considered").

E. *Consideration of Comparable Special Master Decisions*

In reaching a decision in this case, I have considered other decisions issued by special masters (including my own) involving similar injuries, vaccines, or circumstances. I also reference

some of those cases in this Decision, in an effort to establish common themes, as well as demonstrate how prior determinations impact my thinking on the present case.

There is no error in doing so. It is certainly correct that prior decision in different cases do not *control* the outcome herein.[33] *Boatmon v. Sec'y of Health & Human Servs.,* 941 F.3d 1351, 1358–59 (Fed. Cir. 2019); *Hanlon v. Sec'y of Health & Human Servs.*, 40 Fed. Cl. 625, 630 (1998). Thus, the fact that another special master reasonably determined elsewhere, on the basis of facts not in evidence in this case, that preponderant evidence supported the conclusion that vaccine X caused petitioner's injury Y does not compel me to reach the same conclusion in *this* case. Different actions present different background medical histories, different experts, and different items of medical literature, and therefore can reasonably result in contrary determinations.

However, it is *equally* the case that special masters reasonably draw upon their experience in resolving Vaccine Act claims. *Doe v. Sec'y of Health & Human Servs.,* 76 Fed. Cl. 328, 338–39 (2007) ("[o]ne reason that proceedings are more expeditious in the hands of special masters is that the special masters have the *expertise and experience to know the type of information that is most probative of a claim*") (emphasis added). They would therefore be remiss in ignoring prior cases presenting similar theories or factual circumstances, along with the reasoning employed in reaching such decisions. This is especially so given that special masters not only routinely hear from the same experts in comparable cases but are also repeatedly offered the *same* items of medical literature regarding certain common causation theories. It defies reason and logic to obligate special masters to "reinvent the wheel", so to speak, in each new case before them, paying no heed at all to how their colleagues past and present have addressed similar causation theories or fact patterns. It is for this reason that prior decisions can have high persuasive value—and why special masters often explain how a new determination relates to such past decisions.[34] Even if the Federal Circuit does not *require* special masters to distinguish other relevant cases (*Boatmon,* 941 F.3d at 1358), it is still *wise* to do so.

[33] By contrast, Federal Circuit rulings concerning legal issues are binding on special masters. *Guillory v. Sec'y of Health & Human Servs.*, 59 Fed. Cl. 121, 124 (2003), *aff'd* 104 F. Appx. 712 (Fed. Cir. 2004); *see also Spooner v. Sec'y of Health & Human Servs.*, No. 13-159V, 2014 WL 504728, at *7 n.12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014). Special masters are also bound within a specific case by determinations made by judges of the Court of Federal Claims after a motion for review is resolved.

[34] Consideration of prior determinations is a two-way street that does not only inure to the benefit of one party. Thus, I would likely take into account the numerous decisions finding no association between vaccination and autism when confronted with a new claim asserting autism as an injury, and have informed such claimants early in the life of their case that the claim was not viable for just that reason. But I would *also* deem a non-Table claim asserting Guillain-Barré syndrome ("GBS") after receipt of the flu vaccine as not requiring extensive proof on *Althen* prong one "can cause" matters, for the simple reason that the Program has repeatedly litigated the issue in favor of petitioners.

ANALYSIS

I. Overview of Some Prior Flu Vaccine-Death Cases

Other petitioners have succeeded in establishing that certain vaccines, including the flu vaccine, could contribute to an individual's subsequent death.[35] The circumstances of such cases, however, are distinguishable from the present record. *See, e.g., Halverson v. Sec'y of Health & Human Servs.,* No. 15-227V, 2020 WL 992588 (Fed. Cl. Spec. Mstr. Feb. 4, 2020); *Bragg v. Sec'y of Health & Human Servs*., No. 08-477V, 2012 WL 404773 (Fed. Cl. Spec. Mstr. Jan 18, 2012).

In *Halverson,* for example, a petitioner successfully established that a "high dose" version of the flu vaccine (a form often administered to the elderly) was a substantial factor in causing the death of a 66 year-old woman four days after the vaccine's administration. *Halverson*, 2020 WL 992588, at *1. The deceased individual presented with a number of comorbidities comparable to the facts herein, such as diabetes, and had a documented history of cardiac issues. *Id.* at *5–9. She also displayed immediate health degeneration the evening after receiving the vaccine. *Id.* at *9. The special master ruling in the case ultimately determined that the vaccine likely interacted with an upper respiratory infection to significantly aggravate her preexisting heart disease, leading to cardiac arrest and death. *Id.* at *32. *Halverson* thus involved a demonstrably shorter timeframe in which the vaccine could interact with the decedent's preexisting health issues, plus a more potent formulation of the flu vaccine.

In *Bragg,* a petitioner successfully established that a flu vaccine caused the death of an 82 year-old man five days later. *Bragg*, 2012 WL 404773, at *1, *27. The deceased man presented with some comorbidities that are also comparable to the instant case—e.g., prediabetes and hyperlipidemia. *Id.* at *1. But, unlike the present case, the decedent was comparatively in far better health, and reported walking nine miles per day and riding an exercise bike to stay in shape about ten days before his death. *Id.* In addition, and similar to *Halverson,* the decedent in *Bragg* displayed immediate health degeneration 30 minutes after receiving the vaccine, "[h]e never felt any better but continued to get worse until he died." *Id.* at *26. The special master thus found that petitioner had proven that the flu vaccine can cause systemic inflammatory response syndrome in the elderly, that the decedent had suffered from systemic inflammatory response syndrome, and that the injury

[35] There are also cases in which petitioners have successfully established that the flu vaccine caused GBS, which in turn was determined to be a substantial factor in causing the injured party's death. *See*, e.g., *Stitt v. Sec'y of Health & Human Servs*., No. 09-653V, 2013 WL 3356791 (Fed. Cl. Spec. Mstr. May 31, 2013). But such cases provide little guidance herein, since they involved not only circumstances in which the vaccine was alleged to be causal of a specific and discrete illness (and in the case of GBS, an injury *well-understood* to be associated with the flu vaccine), but distinguishable causal mechanisms as well.

occurred in a medically acceptable timeframe. *See id.* at *21–*26.[36] *Bragg* thus also presents a far more compressed timeframe than is at issue herein.

II. Mr. Martin Likely Experienced Bronchopneumonia Caused by an Unidentified Bacterial Infection

In many Vaccine Program cases, a critical first step is to determine the injury at issue—especially when the causal theory depends directly on such a finding. *Broekelschen*, 618 F.3d at 1346. Here, Mr. Martin's death is the ultimate "injury," although Petitioner's theory of how it came about (non-infectious inflammation in a susceptible, immune-compromised individual) is broad enough to encompass whatever the contributing factors causing death were. In addition, Petitioner does not contest that Mr. Martin's established comorbidities (in particular uncontrolled diabetes) likely impacted his health and/or immune response. Respondent, however, has maintained that Mr. Martin likely was experiencing a bacterial pneumonia as of his death, and a finding on this issue does bear on the overall success of Petitioner's causal showing, so I will preliminary resolve this question.

The record in this case preponderates in favor of a finding that Mr. Martin more likely than not had experienced a bacterial infection-driven bronchopneumonia right around the time of his death—and that this illness was integral in causing death. The records from the date of Mr. Martin's untimely death, plus the subsequent pathology report (which stressed the importance of the bronchopneumonia findings), strongly support that conclusion. Dr. Vargas's experienced and cogent review of the lung tissue slides (and specifically what they demonstrated about evidence of neutrophil infiltration and dissemination in Mr. Martin's lungs) only underscored my determination. Her explanation of what she saw from the pattern of inflammation, as well as the very existence of neutrophils (which would more likely than not appear in response to a bacterial infection) was persuasive. In addition, some of the other factual evidence—that Mr. Martin displayed breathing issues right around the time of death, was coughing before his collapse, and was reported to treaters by Petitioner to have been sick around the time of his death—all are consistent with my conclusion.

By contrast, the record evidence does not preponderantly establish that Mr. Martin had been experiencing a non-infectious inflammatory process at any time between the date of vaccination and his death, or that such a process contributed to a bacterial infection-driven bronchopneumonia. There is no particular evidence (other than the uncorroborated claims that Mr. Martin began to feel unwell a few days after the vaccination) that he was experiencing any such

[36] Notably, Dr. Levin was an expert witness for the *Bragg* petitioner. *Bragg*, 2012 WL 404773, at *15. He opined that a cytokine storm caused the petitioner to develop systemic inflammatory response syndrome and later die. *See id.* Here, however, and as noted in more detail below, I do not find him as credible as the special master did in that case, and also deem his opinion on cytokine function generally not to be reliably established, at least given the evidence presented herein.

prior chronic inflammation, regardless of its cause. Moreover, Dr. Levin's interpretation of the pathology report and tissue slides was not nearly as persuasive as Dr. Vargas's, and his arguments that Petitioner had likely only experienced a non-infectious pneumonitis[37] was not evidentiarily supported as the best explanation for his death.

The fact that no particular bacterial agent was ever identified as causal does not cut against my finding. Respondent's experts persuasively established that this is not uncommon—a conclusion bulwarked by Petitioner's own literature. S. Sethi, *Community-Acquired Pneumonia*, Merck Manuals, https://www.merckmanuals.com/professional/pulmonary-disorders/pneumonia/community-acquired-pneumonia (last visited July 13, 2020), filed as Ex. 18 (ECF No. 13-9) at 1 ("even with testing, specific agents are identified in < 50% of cases"). Illnesses can often have an idiopathic viral or bacterial origin, and it is well-understood in the Program that an inability to identify the precise alternative cause of a particular post-vaccination injury does not mean such an explanation is unlikely—any more than it means a vaccine known to have been administered was more likely to have been causal. *Zumwalt v. Sec'y of Health & Human Servs*., No. 16-994V, 2019 WL 1953739, at *19 ("a Vaccine Program petitioner does not succeed in his claim simply by eliminating other possible causes" (citations omitted)) (Fed. Cl. Spec. Mstr. Mar. 21, 2019), *mot. for review den'd,* 146 Fed. Cl. 525 (2019). The overall record best supports the conclusion that Mr. Martin did experience bronchopneumonia, and that it played a significant role in causing his death.

II. Petitioner has not Carried Her Burden of Proof

A. *Althen* Prong One

Petitioner made a number of individual plausible assertions in support of her causation theory, but nevertheless fell short of establishing *preponderantly*, with reference to reliable scientific/medical evidence, that the flu vaccine could cause, or set the stage for, death through a noninfectious inflammatory process driven by vaccine-induced cytokines generated as part of the innate immune response.

Reliable science supports *certain* components of Petitioner's theory. It has been reliably established that (a) vaccines stimulate an innate immune response resulting in the production of

[37] I also did not find convincing Petitioner's arguments that Dr. Collins conceded, in whole or even part, that a non-infectious pneumonitis attributable to aspiration of food particles was the most likely cause of Mr. Martin's death. *See, e.g.*, Pet'r's Br. at 6–7. Unquestionably Dr. Collins *mentioned* pathologic findings supportive of pneumonitis in her reports, as Petitioner observed. However, she also referenced a bacterial pneumonia, did not weight the former over the latter, and at hearing seems to have given more weight to Dr. Vargas's testimony on this issue. In any event, I find based on an *overall review* of the evidence (which is not limited only to written expert reports) that bronchopneumonia is the most evidentiarily-supported conclusion. This determination places greater weight on Dr. Vargas's testimony – as I am free to do, having heard all expert testimony, considered their reports, and weighed the probative value overall of their opinions.

cytokines, including those that are proinflammatory, (b) different cytokines can be sustained at higher-than-normal levels for different periods of time after vaccination, and (c) certain proinflammatory cytokines are associated with some pathologic disease processes. Similarly, there are several non-infectious respiratory diseases propelled by inflammation, such as obstructive lung disease. Petitioner also offered some items of reliable literature, like Cowling, supporting the conclusion that in at least some populations (though clearly *not* in the age cohort most relevant to Mr. Martin) receipt of a flu vaccine can later be associated with other kinds of *viral* respiratory infections (as opposed to bacterial-caused conditions, like bronchopneumonia). And Petitioner's experts pointed to a few case reports (a kind of evidence having some weak probative causation value) in which a flu vaccine preceded damage to the lungs, or invoked (although it was never corroborated with the necessary back-up documentation) VAERS reports purporting instances of post-flu vaccine injuries resulting in death or pneumonia. It is also true that bacterial infectious illnesses, like pneumonia, can be secondary to a viral flu infection. Hamborsky at 190.

But this patchwork showing was not enough, collectively, to constitute preponderant evidence that the flu vaccine could create circumstances ripe for a bacterial-initiated bronchopneumonia occurring weeks later. First, Petitioner's argument relies on scientifically unreliable contentions that confuse cytokine function with expression, and that specifically assume cytokines stimulated by vaccination readily play a pathologic role, even in the absence of an ongoing infectious disease process. Indeed, Dr. Levin himself admitted that the inactivated form of flu vaccine received by Mr. Martin was *unlikely* to cause cytokine overproduction (thus contrasting it with the high dose form deemed to be causal in *Halverson*). Tr. at 45.

Many other petitioners have similarly attempted to satisfy the first *Althen* prong by arguing, as here, that the intended pro-inflammatory impact of a vaccine (to the extent the vaccine stimulates cytokine production in order to create adaptive immune system memory of a viral antigen) can become pathologic. But I have consistently found this argument lacking in sufficient reliable scientific/medical support. *See, e.g.*, *Olson v. Sec'y of Health & Human Servs.*, No. 13-439V, 2017 WL 3624085, at *20 (Fed. Cl. Spec. Mstr. July 14, 2017) ("it remains a speculative issue as to whether cytokine production instigated by a single vaccine containing alum[38] would be robust enough, and occur for long enough, to be pathogenic generally, let alone to cause" the complained-of injury), *mot. for review den'd*, 135 Fed. Cl. 670 (2017), *aff'd*, 758 F. App'x 919 (Fed. Cir. 2018). There is a vast difference between the transient increase in cytokines that vaccination is intended to trigger (since an innate response is required for the vaccine to have immunogenicity) and the kind of *harmful, ongoing inflammatory process* that a wild infection causes. There is an even a greater gap between transient cytokine upregulation due to vaccination

[38] Indeed, there is *no* adjuvant contained in the inactivated form of flu vaccine Mr. Martin received, further diminishing the possibility of a heightened immune response in this case (since adjuvants are intended to spark a more robust response).

and a true "cytokine storm"[39] capable of causing critical and overwhelming systemic damage to an individual. I have yet to be presented with evidence in a Program case linking *any* vaccine to over-production of cytokines capable of becoming pathologic (at least over an extended period of time, as here) simply due to the vaccine's stimulation of an innate immune response—and this case was no different.

Second, Petitioner's theory did not persuasively establish by a preponderance that the flu vaccine could initiate a *non-infectious* inflammatory process that would unfold over time, and later "set up" a person with a high susceptibility to experience a secondary bacterial infection of the kind I have found Mr. Martin experienced. Although evidence was filed in this matter establishing that non-infectious inflammatory processes exist, the evidence linking the flu vaccine – or any vaccine – to such processes was far more limited, and mostly came from the conclusory statements of Petitioner's experts (whom, as discussed below, either lacked the demonstrated experiential depth in their fields necessary to render a reliable opinion, or were unpersuasive for other reasons). Petitioner did file some intriguing and facially-reliable items like Cowling that point to the flu vaccine as possibly having the capacity to reduce an individual's innate resistance to subsequent *viral* respiratory infection. But these articles do not say anything about pneumonia or bacterial infections, and are also distinguishable in terms of the studied population.

Finally, I credit the point that a person with significant comorbidities, such as diabetes, might well be immunocompromised, and therefore might *plausibly* be more likely to have difficulty processing vaccination. But I do not find that it has been preponderantly established in this case that the flu vaccine of the type administered would be expected to have *greater* pathologic potential (and specifically could initiate a non-infectious inflammatory process under such circumstances) for that kind of person, leading to "immunologic dissonance" as argued by Petitioner that would set the stage for a subsequent bacterial infection. Petitioner's Pre-Hearing Brief, dated November 5, 2019 (ECF No. 29) ("Brief"), at 3. Indeed, much of Petitioner's literature stands for the *opposite* conclusion—that vaccines are *expressly recommended* for persons with substantial comorbidities, given the greater risk of a wild viral or bacterial infection the immune-compromised face. *See, e.g.*, E. Bernstein et al., *Cytokine Production After Influenza Vaccination in a Healthy Elderly Population* 16(18) Vaccine 1729–30 (1998), filed on Nov. 27, 2017 as Ex. 19 (ECF No. 13-10).

[39] Indeed, the ongoing COVID-19 pandemic dramatically illustrates what a true cytokine storm looks like, and its fatal implications. Qing Ye et al., *The Pathogenesis and Treatment of the 'Cytokine Storm' in COVID-19*, 80(6) J. of Infection 607–13 (2020). It takes an uncontrolled infectious process, resistant to the functioning of a normal immune response, to produce wildly aberrant cytokine function sufficient to cause death.

The validity of this conclusion is strengthened when the version of the flu vaccine at issue is taken into account. Mr. Martin received a nonadjuvanted[40] version of the flu vaccine, which included inactivated viral particles that would not be able to replicate after injection. Unlike a high dose version of the same vaccine found to be contributing to death in *Halverson*, here it is far less likely that the version in question would have the same capacity, even for a person with significant comorbidities and/or who was deemed immunocompromised.

Petitioner's experts were unable to rectify the deficiencies in the causation theory through the persuasiveness or compelling character of their testimony. Dr. Levin's overall credibility as a trustworthy expert has been called into question in numerous prior cases—by me as well as other special masters.[41] And even if I ignore his past performance and the conclusory, non-credible statements he has repeatedly made elsewhere, I note that his overall expertise in immunologic matters[42] (especially lacking now that his focus is on attorney work) was too lacking herein to imbue his opinions with heft that they could not otherwise obtain from the filed medical literature. His views on the pathology issues relevant to this case were especially outclassed by Dr. Vargas's far more probative and compelling testimony.

Dr. Goldstein, by contrast, did not present the same kind of facial credibility problems, and his testimony and opinions arose mainly from his demonstrated experience treating respiratory and pulmonary diseases. However, Dr. Goldstein ultimately lacked the kind of specific expertise in the immunologic issues most relevant to Petitioner's causation theory to carry the day. The fact that he could rely on some treating expertise in offering an opinion on the causal link in this case between vaccination and Mr. Martin's later death had evidentiary value, but was not enough to carry Petitioner's overall preponderant burden—especially in the absence of other reliable scientific and medical evidence.

In discussing my weighing of the evidence in this case offered in connection with the first *Althen* prong, a distinction should be made between the probative value of the scientific or medical articles discussed and filed to support the claim and expert testimony on these same subjects. It is unquestionably the case (as I have already said above) that petitioners need *not* offer medical

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[40] In immunology an adjuvant is "a nonspecific stimulator of the immune response, such as BCG vaccine." *Dorland's* at 32.

[41] *See*, e.g., *Bigbee v. Sec'y of Health & Human Servs.*, No. 06-663V, 2012 WL 1237759, at *30 (Fed. Cl. Spec. Mstr. Mar. 22, 2012) ("Dr. Levin's testimony in particular was extremely unhelpful—as would be expected from someone who practices law 99% of the time and thus medicine 1% and has not seen a patient since 1993").

[42] This is so even in comparison to Dr. Collins, who unquestionably does not have board certification in immunology, and yet was able to explain the immunologic concepts at issue in this case in a more lucid and persuasive manner. Of course, Dr. Levin today spends far more of his time (when not an expert witness) as an attorney, and his credentials in immunology lie mainly in his educational background—they have not been honed over the years in patient practice or research not relating to a lawsuit in which he was involved.

literature to prevail. *Andreu*, 569 F.3d at 1378–79. Thus, while literature supporting "contention X" may be absent from a case, that fact is not disqualifying of the claim as a whole. Rather, the total mix of evidence can easily meet the preponderant burden even where (as is usually the case, given the rareness of injuries evaluated in the Program) there is no one item of article addressing, let alone proving, that the vaccine in question "can cause" the relevant injury. Expert opinions can assist petitioners in such circumstances by filling in such gaps.

Nevertheless, I am called upon to *weigh* the overall evidence offered in any case, on each *Althen* prong. Moreover, it is equally a black-letter concept that I need not accept an expert's opinion at face value.[43] *Snyder*, 88 Fed. Cl. at 743. Rather, in properly performing my duties, I may consider how probative such opinions are, in light of the expert's credentials, personal experience with the subject, and other considerations that shed light on the opinion's reliability. I may apply the *Daubert* criteria, used in other courts to evaluate the admissibility of evidence, to determine whether an opinion is sufficiently reliable to give it significant probative weight.

Here, I have found that Drs. Levin's and Goldstein's pronouncements were *not* persuasive or sufficiently reliable to fill other gaps in Petitioner's case that could not be satisfied with other forms of evidence. I made this determination after listening to them at trial, reviewing their reports, and weighing the reliability of their statements against other evidence, from both the medical record and the other scientific evidence. Based on this determination, and for the reasons stated above, Petitioner has not carried her *Althen* prong I burden.

B. *Althen* Prong Two

Although (and as stated above) the evidence preponderates in favor of the conclusion that Mr. Martin more likely than not was experiencing a bacterial bronchopneumonia around February 26, 2015, and that it played a significant role in his untimely death, I do not purport to identify the *precise* cause of his death, given the swirl of contributory factors at issue. For example, the records could be read to support cardiac arrest as the immediate cause—although I cannot ultimately conclude that such heart issues were the product of his illness, his preexisting uncontrolled diabetes, or some inter-relationship between the two. However, whatever the cause, the evidence in this case does *not* preponderantly establish that the flu vaccine he received three weeks before played any role at all in his death.

The medical record preponderantly establishes at a minimum that Mr. Martin had felt sick in the days immediately *before* his death, as corroborated by contemporaneous statements made

[43] Were it otherwise, there would never be any need in the Program for special masters to consider an expert's credibility and persuasiveness. Once a petitioner obtained an expert opinion, the first prong would be automatically satisfied. Although many petitioners essentially embrace this standard on appeal (when they argue that a special master has not given proper weight to an expert opinion—mainly because the special master did not *accept* the opinion offered), this cannot possibly be accurate.

by Petitioner to emergency treaters. Mrs. Martin's description of Mr. Martin's condition immediately prior to his collapse also paints a picture of an individual who did not feel well, and may also have been experiencing some respiratory difficulties. All of the above, when supplemented with the pathologic findings and immediate ER testing, are consistent with an individual suffering from an undiagnosed bacteria infection-induced pneumonia, whose existing comorbidities inhibited greatly his ability to respond positively to such negative stimulants.

But that same record does not persuasively establish any connection between Mr. Martin's health at the time of his death and how he may have been after receipt of the flu vaccine approximately *three weeks before*. Thus, there is no evidence that Mr. Martin experienced any kind of close-in-time (meaning within a day or two) malaise, fever, or other reaction to the vaccination, as even Petitioner has admitted. Br. at 9. At most, she maintains that no sooner than *three* days after vaccination, Mr. Martin began feeling unwell (albeit with many symptoms that are not specific for pneumonia)—but these assertions are wholly uncorroborated by any other evidence, and thus amount to bare allegations that do not preponderantly establish the fact for which they have been offered. Section 13(a)(1(B) (Program claimants cannot succeed solely on the basis of claims "unsubstantiated by medical records or by medical opinion"). And, as Dr. Collins noted, some of these symptoms Petitioner alleged her husband experienced (such as nausea or diarrhea) were generally nonspecific, or described GI-associated problems that are not precursors of a bacterial lung infection.

In addition, the record does not corroborate that Mr. Martin felt unwell (in a way distinguishable from his usual circumstances) for most of the period thereafter. At no time in this period before Mr. Martin had his telehealth caregiver visit[44] on February 24th (meaning no more than two and one-half weeks from the alleged onset to the latter date) does the record reveal any attempt even to seek treatment of any kind. The record better supports the conclusion that he felt unwell *very close in time* to the date of his death—but that is consistent with him experiencing an acute bronchopneumonia, distinguishable from his alleged condition three to five days post-vaccination. And although I credit somewhat Petitioner's assertion that poor winter weather may have prevented him from seeking treatment despite a desire to do so, this overall timeframe is too long, and too otherwise unilluminating about any flu-like symptoms he may have been experiencing, to conclude more likely than not that he felt sick for this *entire* period, beginning a few days after vaccination.[45]

[44] In addition, and as Respondent pointed out, Mr. Martin did not inform this telehealth treater that he did not feel well—although given the primary purpose of that visit (which obviously from the record was focused on Mr. Martin's diabetes), it is reasonable to infer that he would not necessarily have expected to discuss that aspect of his health at that time.

[45] While Petitioner correctly noted that some of the records contemporaneous with Mr. Martin's death employed the temporally-vague term of "days" to measure how long Petitioner had told emergency treaters he felt unwell, and while it is true that this indeterminate term *could* be read to mean a period longer than a few days, I do not find that the

This record thus is inconsistent with the contentions of Petitioner's experts that Mr. Martin began to experience a non-infectious inflammatory process a few days post-vaccination, setting the stage for his subsequent death three weeks later. Insufficient record evidence establishes that he was experiencing *any* inflammatory processes in this time period, and Dr. Vargas persuasively opined that the pathology evidence from after death did not reveal the presence of a prior chronic process of lung inflammation. There is no evidence of a cytokine storm-like process that was occurring over such a lengthy period, brought on by pro-inflammatory cytokines stimulated by vaccination.[46] On the basis of this record, the evidence best supports the conclusion that Petitioner's death was attributable to a combination of the bronchopneumonia and his preexisting health conditions - the pathologic effect of vaccination was not even necessary to cause the same tragic result.

I additionally note some other findings relevant to the second "did cause" prong. First, Petitioner has not preponderantly established that the flu vaccine was contraindicated for Mr. Martin. Although one record from the time of his death so suggests, the record *contemporaneous* with his receipt of the vaccine at issue explicitly establishes his consent to the vaccine, and his affirmation suggests at least his own understanding that it was *not* contraindicated. Ex. 5 at 115 (denying contradictions on the day flu vaccine was received); Ex. 7 at 154 (listing contradictions to the flu vaccine 21 days after its receipt). While Mr. Martin's consent is not equivalent to a health assessment of the safety of the vaccine for someone in comparable poor health, it undercuts Petitioner's contrary assertions to some degree. The record also establishes Petitioner's recollection that Mr. Martin's physician *recommended* receipt of the flu vaccine precisely because of his diabetes. Tr. at 10–11. This greatly undercuts Petitioner's other contentions about the dangers of immunocompromised individuals like Mr. Martin receiving vaccinations (which do not otherwise find evidentiary support, as discussed above).

Second (and related to the latter point), Petitioner has not corroborated her contentions (relied upon by her experts) that Mr. Martin experienced an aberrant reaction to the earlier 2013 vaccination (a point Petitioner seemed to raise in the interests of underscoring the impact the

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record overall supports that interpretation, given the lack of evidence corroborating Mrs. Martin's contention that her husband felt flu-like for *most* of the three-plus week temporal interval from 2–3 days post-vaccination to his death.

[46] Indeed, as Dr. Collins noted, the best evidence in this case that Mr. Martin might have experienced a debilitating, uncontrolled inflammatory cytokine storm of the kind Dr. Levin proposed had occurred could only be derived from the fact that (a) treaters proposed sepsis associated with the bacterial infection causing his bronchopneumonia as potentially explaining his cardiac arrest, and (b) certain literature filed in the case, like Boomer, associates cytokine storms with sepsis. Ex. 5 at 341; Ex. 7 at 11; Tr. at 320–21. Yet the record does not support a finding of sepsis anytime before right around Mr. Martin's death—*not* in the two or three weeks post-vaccination. The record thus does not allow the conclusion that the sepsis speculated to be connected to Mr. Martin's death was in any manner vaccine-related (even assuming that a vaccine *could* produce a cytokine storm—a contention not established herein).

vaccine may have had on him, perhaps in a challenge-rechallenge sense).[47] There is no record evidence at all confirming this assertion. Although I found Petitioner to be sincere in her testimony overall, these specific contentions were not corroborated by independent evidence. I thus do not find that allegations of a purported earlier vaccine reaction made a second reaction more likely, and Petitioner's experts did not reasonably rely on this unproven assertion in formulating their opinions. *See, e.g., Dobrydnev*, 566 F. App'x at 982–83 (holding that the special master was correct in noting that "when an expert assumes facts that are not supported by a preponderance of the evidence, a finder of fact may properly reject the expert's opinion") (citing *Brooke Group Ltd. v. Brown & Williamson Tobacco Corp.*, 509 U.S. 209, 242 (1993)). And similar to the 2015 vaccination, the record of the 2013 flu vaccine administration also memorializes Mr. Martin's consent and agreement that he appropriately should receive it. Ex. 5 at 241 (denying contradictions to flu vaccine in 2013).

C. *Althen* Prong Three

Petitioner did not establish herein that the two timeframe "legs" in this case—from vaccination to purported onset within three to five days thereafter, and then from onset to Mr. Martin's death—were medically acceptable for causation purposes.

First, the most persuasive and reliable scientific or medical literature offered in this case supports the conclusion that post-flu vaccine malaise (reflecting a reaction to vaccination and perhaps the effects of the proinflammatory cytokines pointed to by Petitioner's experts) would begin in the somewhat shorter timeframe of no more than a day or two. Centers for Disease Control and Prevention, *Epidemiology and Prevention of Vaccine Preventable Diseases* 200–01 Jennifer Hamborsky et al. eds., (2015), filed on Feb. 27, 2019 as Ex. Y (ECF No. 26-3) (pages 25–26 of Ex. Y). Yet Mr. Martin had no demonstrated reaction *at all* to the vaccine in that timeframe, as Petitioner has admitted. I also do not find that it has been preponderantly established that he ever experienced a similar reaction to a prior receipt of the flu vaccine, such that he would have been expected to have an even more rapid reaction after his next vaccine exposure. As a result, the evidence is thin to begin with that the flu vaccine had begun to cause a non-infectious inflammatory process for Mr. Martin within a few days of its administration.

Second, even if Mr. Martin *had* experienced a documented, flu-like reaction closer in time to vaccination (or if the difference between a three and two-day onset is discounted for sake of argument), Petitioner has not offered sufficient reliable evidence to support the conclusion that the

[47] Other special masters have described "rechallenge" as follows: "[c]hallenge-rechallenge happens when a person (1) is exposed to one antigen, (2) reacts to that antigen in a particular way, (3) is given the same antigen again, and (4) reacts to that antigen similarly. Typically, the second reaction is faster and more severe." *Nussman v. Sec'y of Health & Human Servs.*, 83 Fed. Cl. 111, 119 (Fed. Cl. 2008) (internal citations omitted) (quoting *Nussman v. Sec'y of Health & Human Servs.*, No. 99-500V, 2008 WL 449656, at *9 (Fed. Cl. Spec. Mstr. Jan. 31, 2008)).

flu vaccine could initiate a non-infectious inflammatory process, fueled by cytokine upregulation, that would persist over a 16 to 17 day-period sufficient to play a role in causing his death later. The evidence Petitioner's experts relied upon to establish this point did *not* support the contention that a one-time vaccination can launch the chronic production of pro-inflammatory cytokines over such a timeframe. At best, Petitioner references Mohanty, which concludes that the production of two kinds of pro-inflammatory cytokines (Il-6 and TNF-α) are in fact *impaired* in older individuals, while Il-10 (an *anti-inflammatory* cytokine) is dysregulated and increases for 7–28 days post vaccination in older individuals. Mohanty at 1179, 1183. This hardly establishes the lingering and pathologic effects of post-vaccination pro-inflammatory cytokine upregulation. And neither of Petitioner's experts possessed the specific, demonstrated expertise in immunologic matters to persuasively establish such arguments in any event.[48]

The other facts of the case also greatly undercut Petitioner's contentions about timeframe. There is no record evidence that Mr. Martin was experiencing any kind of inflammatory process, infectious in origin or not, in the two to three-week period before his death. The nonspecific symptoms he is alleged to have displayed also are somewhat consistent with his existing diabetes—a proposition that was not effectively rebutted by Petitioner. And the symptoms he arguably felt in the days before death could easily be attributed to the post-mortem bronchopneumonia diagnosis revealed in the pathology results. The overall three-week timeframe from vaccination to death, with no intervening evidence of medical treatment, corroborative test results, or other objective proof consistent with Petitioner's theories, is too long to deem medically acceptable, given the high likelihood of other contingencies, known and unknown, that could also have played a role in Petitioner's death.

III. The Flu Vaccine was not a Substantial Factor in Mr. Martin's Death

Because of the aforementioned timeframe issues, this case unquestionably does not present circumstances in which I could find (based on what is often deemed a "*Shyface* analysis") that the flu vaccine was a substantial factor in Mr. Martin's illness and death, even if the predominating factor cannot be identified. *Shyface*, 165 F.3d at 1352–53. In *Shyface*, the Federal Circuit found that although a child's death was associated with a fever that could equally be attributed to both a vaccine or *E. coli* infection that the child was suffering from at the time of vaccination, the fact that one could not be established over the other as most likely causal did not preclude a recovery for the claimant. *Id.* at 1351, 1353. The special master in *Halverson* found such reasoning persuasive in determining that the high dose flu vaccine was causal of an individual's death despite the decedent's demonstrated comorbidities. *Halverson*, 2020 WL 992588, at *26.

[48] Cases like *Halverson*, by contrast, involve a compressed timeframe of less than a week from the date of vaccination to death, and thus a period in which it would be far more credible and persuasive that the vaccine's intended cytokine stimulation could negatively interact with a person's existing comorbidities sufficient to contribute to a pathologic process resulting in death. *Halverson*, 2020 WL 992588, at *1 (vaccine received four days before death).

Here, by contrast, the facts are wholly different. The *Halverson* decedent's vaccination occurred far closer in time to death, and there was robust evidence of an immediate reaction or pre-death illness, thus allowing for the possibility that the vaccine played some contributory role. But in this case, the period from even alleged onset (no sooner than February 8, 2015) to the morning of February 26, 2015, is too attenuated, and without suggestion of any specific medical problems other than Mr. Martin's ongoing struggle to control his diabetes, plus some evidence that he might have begun to experience pneumonia symptoms right before his death. And Petitioner's experts did not persuasively establish that the flu vaccine could create circumstances that would interact with a person with Mr. Martin's comorbidities over such a several-week period, contributing to his death even if a bacterial infection was the likely immediate cause. It cannot be concluded here that the flu vaccine likely played any role in Mr. Martin's death.

CONCLUSION

Petitioner has not carried her burden of proof, and therefore she is not entitled to an award of compensation in this case. In the absence of a motion for review filed pursuant to RCFC Appendix B, the clerk of the court **SHALL ENTER JUDGMENT** in accordance with the terms of this decision.[49]

IT IS SO ORDERED.

s/ Brian H. Corcoran
Brian H. Corcoran,
Chief Special Master

[49] Pursuant to Vaccine Rule 11(a), the parties may expedite entry of judgment if (jointly or separately) they file notices renouncing their right to seek review.

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Review

The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19

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SUMMARY

Cytokine storm is a general term applied to maladaptive cytokine release in response to infection and other stimuli. The pathogenesis is complex but includes loss of regulatory control of proinflammatory cytokine production, both at local and systemic levels. The disease progresses rapidly, and the mortality is high. Some evidence shows that, during the coronavirus disease 2019 (COVID-19) epidemic, severe deterioration in some patients has been closely associated with dysregulated and excessive cytokine release. This article reviews what we know of the mechanism and treatment strategies of the COVID-19 virus-induced inflammatory storm in an attempt to provide some background to inform future guidance for clinical treatment.

Introduction

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) emerged for the first time in Wuhan, China, in December 2019. It is a type of highly pathogenic human coronavirus (HCoV) that causes zoonotic diseases and poses a major threat to public health. The vast majority of patients with the coronavirus disease 2019 (COVID-19) have had a good prognosis, but there were still some critical individuals and even deaths.[1]

Most of these critically ill and dead patients did not develop severe clinical manifestations in the early stages of the disease. Some of the patients only showed mild fever, cough, or muscle soreness. The conditions of these patients deteriorated suddenly in the later stages of the disease or in the process of recovery. Acute respiratory distress syndrome (ARDS) and multiple-organ failure occurred rapidly, resulting in death within a short time.[2] Cytokine storm is considered to be one of the major causes of ARDS and multiple-organ failure.[3] It plays an important role in the process of disease aggravation.[4] Clinical studies have detected a cytokine storm in critical patients with COVID-19. Therefore, effectively suppressing the cytokine storm is an important way to prevent the deterioration of patients with COVID-19 infection and save the patients' lives.[5] This article reviews the mechanisms by which HCoV infection induces cytokine storm and the options to inhibit the cytokine storm, in order to provide a reference for the clinical diagnosis and treatment of COVID-19.

HCoVs

Coronaviruses (CoVs) are single-stranded, positive-strand RNA viruses belonging to the Coronaviridae family, Nidovirales order. The International Committee on Taxonomy of Viruses (ICTV) classifies the CoVs into four categories: α, β, γ, and δ. Under the electron microscope, the virus particles display a rough spherical or multi-faceted crystal shape. The surface of the viruses has prominent club-shaped projections composed of its spike protein. Inside the virus particle is the viral genome wrapped in a nucleocapsid. The viral genome contains approximately 26,000 to 32,000 bases. CoVs are the largest known RNA viruses. The positive-strand viral RNA consists of a cap structure at the 5′ end and multiple poly(A) tails at the 3′ end. It serves as messenger RNA (mRNA), allowing the translation of replicase/transcriptase and viral structural proteins. The replicase/transcriptase genes account for approximately 2/3 of the 5′-end RNA sequence and are composed of two overlapping open reading frames (ORFs): ORF1a and ORF1b. The ORFs encode 16 non-structural proteins. The remaining 1/3 of the RNA sequence encodes four classical viral structural proteins, namely, spike (S) protein, envelope (E) protein, membrane (M) protein, and nucleocapsid (N) protein. In addition, genes encoding some viral accessory proteins are interspersed in the coding regions of the viral structural proteins. The coding sites and number of these accessory protein genes are an important basis for CoV classification. CoVs can infect a variety of host species, including birds, humans and some other vertebrates. These viruses mainly cause respiratory and intestinal infections and induce a variety of clinical manifestations.[6,7]

Coronaviruses have long been recognized as important pathogens that infect the respiratory tracts of domestic and com-

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panion animals and are the causes of mild and severe respiratory diseases in humans.[7,8] So far, seven HCoVs that can invade humans have been identified, including the α-type HCoV-229E and HCoV-NL63; the β-type HCoV-HKU1, SARS-CoV, MERS-CoV, and HCoV-OC43; and 2019-nCoV, causing the present epidemic. According to their pathogenicity, HCoVs are divided into mildly pathogenic HCoVs (including HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU) and highly pathogenic CoVs (including severe acute respiratory syndrome CoV (SARS-CoV),[9] Middle East respiratory syndrome coronavirus (MERS-CoV) [10,11] and SARS-CoV-2). The mildly pathogenic HCoVs infect the upper respiratory tract and cause seasonal, mild to moderate cold-like respiratory diseases in healthy individuals. In contrast, the highly pathogenic HCoVs (hereinafter referred to as pathogenic HCoVs or HCoVs) infect the lower respiratory tract and cause severe pneumonia, sometimes leading to fatal acute lung injury (ALI) and ARDS. The pathogenic HCoVs have high morbidity and mortality and pose a major threat to public health.[12–14]

Mechanism of cytokine storm by pathogenic HCoV infection

It has long been believed that cytokines play an important role in immunopathology during viral infection. A rapid and well-coordinated innate immune response is the first line of defense against viral infection. However, dysregulated and excessive immune responses may cause immune damage to the human body.[15–17] The relevant evidences from severely ill patients with HCoVs suggest that proinflammatory responses play a role in the pathogenesis of HCoVs. *In vitro* cell experiments show that delayed release of cytokines and chemokines occurs in respiratory epithelial cells, dendritic cells (DCs), and macrophages at the early stage of SARS-CoV infection. Later, the cells secrete low levels of the antiviral factors interferons (IFNs) and high levels of proinflammatory cytokines (interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)) and chemokines (C-C motif chemokine ligand (CCL)-2, CCL-3, and CCL-5).[18–20] Like SARS, MERS-CoV infects human airway epithelial cells, THP-1 cells (a monocyte cell line), human peripheral blood monocyte-derived macrophages and DCs, and induces delayed but elevated levels of proinflammatory cytokines and chemokines.[21,22] After MERS-CoV infection, plasmacytoid dendritic cells, but not mononuclear macrophages and DCs,[23] are induced to produce a large amount of IFNs.

Serum cytokine and chemokine levels are significantly higher in patients with severe MERS than patients with mild to moderate MERS.[24,25] The elevated serum cytokine and chemokine levels in MERS patients are related to the high number of neutrophils and monocytes in the patients' lung tissues and peripheral blood, suggesting that these cells may play a role in lung pathology.[24–26] Similar phenomena have been observed in patients with SARS-CoV infection.[27–34] The production of IFN-I or IFN-α/β is the key natural immune defense response against viral infections, and IFN-I is the key molecule that plays an antiviral role in the early stages of viral infection.[35,36] Delayed release of IFNs in the early stages of SARS-CoV and MERS-CoV infection hinders the body's antiviral response.[36] Afterward, the rapidly increased cytokines and chemokines attract many inflammatory cells, such as neutrophils and monocytes, resulting in excessive infiltration of the inflammatory cells into lung tissue and thus lung injury. It appears from these studies that dysregulated and/or exaggerated cytokine and chemokine responses by SARS-CoV-infected or MERS-CoV-infected cells could play an important role in pathogenesis of SARS or MERS.

Animal models can well elucidate the role of cytokines and chemokines in mediating pulmonary immunopathology after HCoV infection. Despite of similar virus titers in the respiratory tract, SARS-CoV-infected old nonhuman primates are more likely to develop immune dysregulation than the infected young primates, leading to more severe disease manifestations.[37] It seems that the excessive inflammatory response rather than the virus titer is more relevant to the death of the old nonhuman primates.[37] Similarly, in BALB/c mice infected with SARS-CoV, disease severity in old mice is related to the early and disproportionately strong upregulation of the ARDS-related inflammatory gene signals.[38] The rapid replication of SARS-CoV in BALB/c mice induces the delayed release of IFN-α/β, which is accompanied by the influx of many pathogenic inflammatory mononuclear macrophages.[15] The accumulated mononuclear macrophages receive activating signals through the IFN-α/β receptors on their surface and produce more monocyte chemoattractants (such as CCL2, CCL7, and CCL12), resulting in the further accumulation of mononuclear macrophages. These mononuclear macrophages produce elevated levels of proinflammatory cytokines (TNF, IL-6, IL1-β, and inducible nitric oxide synthase), thereby increasing the severity of the disease. Depleting inflammatory monocyte-macrophages or neutralizing the inflammatory cytokine TNF protected mice from the fatal SARS-CoV infection. In addition, IFN-α/β or mononuclear macrophage-derived proinflammatory cytokines induce the apoptosis of T cells, which further hinders viral clearance.[15] Another consequence of rapid viral replication and vigorous proinflammatory cytokine/chemokine response is the induction of apoptosis in lung epithelial and endothelial cells. IFN-$\alpha\beta$ and IFN-γ induce inflammatory cell infiltration through mechanisms involving Fas–Fas ligand (FasL) or TRAIL–death receptor 5 (DR5) and cause the apoptosis of airway and alveolar epithelial cells.[39–41] Apoptosis of endothelial cells and epithelial cells damages the pulmonary microvascular and alveolar epithelial cell barriers and causes vascular leakage and alveolar edema, eventually leading to hypoxia in the body. Therefore, inflammatory mediators play a key role in the pathogenesis of ARDS.

ARDS is the leading cause of death in patients infected with SARS-CoV or MERS-CoV.[42,43] It is now known that several proinflammatory cytokines (IL-6, IL-8, IL-1β, granulocyte-macrophage colony-stimulating factor, and reactive oxygen species) and chemokines (such as CCL2, CCL-5, IFNγ-induced protein 10 (IP-10), and CCL3) all contribute to the occurrence of ARDS.[44–46] These results support such points of view that, following SARS-CoV infection, high virus titers and dysregulation of cytokine/chemokine response cause an inflammatory cytokine storm. The inflammatory cytokine storm is accompanied by immunopathological changes in the lungs.

The relationship between cytokine levels and disease progression in patients

High levels of expression of IL-1B, IFN-γ, IP-10, and monocyte chemoattractant protein 1 (MCP-1) have been detected in patients with COVID-19. These inflammatory cytokines may activate the T-helper type 1 (Th1) cell response.[47] Th1 activation is a key event in the activation of specific immunity.[48] However, unlike SARS patients, patients with COVID-19 also have elevated levels of Th2 cell-secreted cytokines (such as IL-4 and IL-10), which inhibit the inflammatory response. The serum levels of IL-2R and IL-6 in patients with COVID-19 are positively correlated with the severity of the disease (i.e., critically ill patients > severely ill patients > ordinary patients).[49] Other studies have found that, compared with COVID-19 patients from general wards, patients in the intensive care unit (ICU) display increased serum levels of granulocyte colony-stimulating factor, IP-10, MCP-1, macrophage inflammatory protein-1A, and TNF-α. The above studies suggest that the cytokine storm is positively correlated with disease severity.[47]

A report on the severe new-type coronavirus-infected pneumonia showed that 37 patients (71.2%) required mechanical ventilation, and 35 patients (67.3%) suffered ARDS. Moreover, the mortality of the elderly patients with ARDS was significantly elevated.[50]

The core pathological change in ARDS is the pulmonary and interstitial tissue damage caused by nonspecific inflammatory cell infiltration.[51] Local excessive release of cytokines is the decisive factor that induces this pathological change and clinical manifestation.[52] In COVID-19, the inflammatory cytokine storm is closely related to the development and progression of ARDS. The serum levels of cytokines are significantly increased in patients with ARDS, and the degree of increase is positively correlated with mortality rate.[53] The cytokine storm is also a key factor in determining the clinical course of extrapulmonary multiple-organ failure.[54] This partially explains the signs of extrapulmonary organ failure (such as elevated liver enzymes and creatinine) seen in some COVID-19 patients without respiratory failure, suggesting that the inflammatory cytokine storm is the cause of damage to extrapulmonary tissues and organs.

In summary, the new-type coronavirus infection causes an inflammatory cytokine storm in patients. The cytokine storm leads to ARDS or extrapulmonary multiple-organ failure and is an important factor that causes COVID-19 exacerbation or even death.

Theoretical treatment strategy with inflammatory cytokine storm

High virus titer and the subsequent strong inflammatory cytokine and chemokine responses are related to the high morbidity and mortality observed during the pathogenic HCoV infection. The experience from treating SARS and MERS shows that reducing viral load through interventions in the early stages of the disease and controlling inflammatory responses through immunomodulators are effective measures to improve the prognosis of HCoV infection.[55–58]

IFN-λ

IFN-λ primarily activates epithelial cells and reduces the mononuclear macrophage-mediated proinflammatory activity of IFN-$\alpha\beta$.[59] In addition, IFN-λ inhibits the recruitment of neutrophils to the sites of inflammation.[60] SARS-CoV and MERS-CoV mainly infect alveolar epithelial cells (AEC). IFN-λ activates the antiviral genes in epithelial cells, thereby exerting antiviral effects without overstimulating the human immune system. Therefore, IFN-λ may be an ideal treatment. Some studies have applied pegylated and non-pegylated interferons for the treatment of HCoVs, but the efficacy varied significantly due to the application of different treatment regimens. Early administration of interferons has certain benefits in reducing viral load and improves the clinical symptoms of patients to a certain extent. However, it fails to reduce mortality rates.[61–63] With the exception of early administration, the use of interferons at other time periods will not bring more benefits than placebo treatment.[63]

Corticosteroid therapies

Corticosteroids are a class of steroid hormones that have anti-inflammatory functions. Corticosteroids are commonly used to suppress inflammation. During the 2003 SARS epidemic, corticosteroids were the primary means of immunomodulation. Timely administration of corticosteroids often leads to early improvements such as reducing fever, relieving radiation infiltration of the lung, and improving oxygenation.[64–66] A retrospective study of 401 patients with severe SARS revealed that proper administration of glucocorticoids in patients with severe SARS significantly reduced the mortality rate and shortened the hospital stay. Moreover, secondary infections and other complications rarely occurred in these glucocorticoid-treated patients.[67] However, there are studies showing that administration of corticosteroid therapy during human SARS-CoV infection led to adverse consequences. Early treatment of SARS patients with corticosteroids increased plasma viral load in non-ICU patients, resulting in the aggravation of the disease.[64]

In treatment of patients with COVID-19, the use of glucocorticoids has again become a major conundrum for clinicians.[68] The timing of administration and the dosage of glucocorticoids are very important to the outcome of the severely ill patients. A too early administration of glucocorticoids inhibits the initiation of the body's immune defense mechanism, thereby increasing the viral load and ultimately leading to adverse consequences. Therefore, glucocorticoids are mainly used in critically ill patients suffering inflammatory cytokine storm. Inhibition of excessive inflammation through timely administration of glucocorticoids in the early stage of inflammatory cytokine storm effectively prevents the occurrence of ARDS and protects the functions of the patients' organs. For patients with progressive deterioration of oxygenation indicators, rapid imaging progress, and excessive inflammatory response, the use of glucocorticoid in the short term (3–5 days) is appropriate, and the recommended dose is no more than equivalent to methylprednisolone 1–2 mg/kg/day.[69] It should be noted that large doses of glucocorticoid may delay the clearance of coronavirus due to immunosuppression.

Intravenous immunoglobulin (IVIG)

Chen et al. analyzed the treatment of 99 Wuhan patients with COVID-19 and found that 27% of these patients had received IVIG treatment.[70] IVIG therapy has the dual effects of immune substitution and immunomodulation. Its practical application value in treatment of COVID-19 needs confirmation in future studies.

IL-1 family antagonists

During the cytokine storm, the three most important cytokines in the IL-1 family are IL-1β, IL-18, and IL-33.[4] Studies that focus on the inhibition of IL-1β to reduce the cytokine storm have attracted most attention. Anakinra, an antagonist of IL-1β, can be used to treat the cytokine storm caused by infection. It significantly improved the 28-day survival rate of patients with severe sepsis.[71] There is currently no clinical experience with applying specific IL-1 family blockers to treat COVID-19. Their effects need to be verified through *in vivo* animal experiments and clinical trials.

IL-6 antagonists

Tocilizumab is an IL-6 antagonist that suppresses the function of the immune system. Currently, tocilizumab is mainly applied in autoimmune diseases such as rheumatoid arthritis.[72] Tocilizumab itself has a therapeutic effect on the infection-induced cytokine storm.[73] Serum IL-6 level is significantly increased in severely ill patients with COVID-19. Clinical studies from China have shown that Tocilizumab is effective in treating severely ill patients with extensive bilateral lung lesions, who have elevated IL-6 levels. The first dose was 4–8 mg/kg. The recommended dosage was 400mg with 0.9% saline diluted to 100 ml. The infusion time was more than 1 h. For patients with poor efficacy of the first dose, an additional dose can be applied after 12 h (the dose is the same as before), with a maximum of two cumulative dose.

TNF blockers

TNFs are key inflammatory factors that trigger a cytokine storm. They are attractive targets for controlling the cytokine storm. A meta-analysis showed that anti-TNF therapy has significantly improved survival in patients with sepsis.[74] Anti-TNF therapy has also achieved satisfactory outcomes in treatment of noninfectious

diseases such as atherosclerosis.[75] Studies in animal models have shown that TNFs contribute significantly to acute lung injury and impair the T cell response in SARS-CoV-challenged mice. In mice, neutralization of TNF activity or loss of TNF receptor provides protection against SARS-CoV-induced morbidity and mortality.[15,76] However, it should be noted that, at least in the later stages of infection, TNF has not been detected in the serum of patients with SARS. At present, TNF blockers have not been suggested in the treatment of patients with COVID-19, but the efficacy of TNF blockers in treatment of patients with COVID-19 deserves further exploration.

IFN-$\alpha\beta$ inhibitors

IFN-$\alpha\beta$ limits viral replication by inducing IFN-stimulated gene. However, IFN-$\alpha\beta$ also exacerbates diseases through enhancing the recruitment and function of mononuclear macrophages and other innate immune cells. Although an early interferon response has a protective effect on mice infected with SARS-CoV, delayed IFN-$\alpha\beta$ signaling causes an imbalance of the anti-SARS-CoV immune responses in humans. This phenomenon indicates that the timing of IFN treatment is crucial to the outcome of diseases. Based on these results, IFN-$\alpha\beta$ receptor blockers or antagonists should be administered in the later stages of severe disease to prevent excessive inflammatory responses.[16]

Chloroquine

Chloroquine inhibits the production and release of TNF and IL-6, which indicates that chloroquine may suppress the cytokine storm in patients infected with COVID-19.[77] Chloroquine phosphate has been used in the treatment of adults aged 18 to 65 in China.[78] The recommended dosage by diagnosis and treatment of new coronavirus pneumonia (trial version 7) from china is as follows: If the weight is more than 50 kg, 500 mg each time, 2 times a day, 7 days as a treatment course; If the weight is less than 50 kg, 500 mg each time on the first and second days, twice a day, 500 mg each time on the third to seventh days, once a day.

Ulinastatin

Ulinastatin is a natural anti-inflammatory substance in the body. It protects the vascular endothelium by inhibiting the production and release of inflammatory mediators. Ulinastatin is widely used in clinical practice to treat pancreatitis and acute circulatory failure. Ulinastatin reduces the levels of proinflammatory factors such as TNF-α, IL-6, and IFN-γ, and increases the level of anti-inflammatory factor IL-10.[79] These activities of ulinastatin promote the balance between proinflammatory and anti-inflammatory responses in humans, thus interrupting the cytokine storm induced by the vicious cycle of inflammation. Animal studies show that the anti-inflammatory effect of high-dose ulinastatin is equivalent to that of hormones.[80] However, unlike glucocorticoids, ulinastatin does not inhibit immune functions and is unlikely to cause sequelae such as femoral head necrosis. Therefore, ulinastatin has great application prospects in the treatment of COVID-19.

The inhibitory effect of oxidized phospholipids (OxPL)

In a mouse model of influenza A virus (IAV) infection, OxPL increases the production of cytokines/chemokines in lung macrophages through the Toll-like receptor 4 (TLR4)–TIR-domain-containing adapter-inducing interferon-β signaling pathway, thereby promoting the occurrence of ALI.[81] Eritoran is a TLR4 antagonist. It does not have direct antiviral activity but has strong immunomodulatory functions. Eritoran effectively lowers the production of OxPL, inflammatory cytokines, and chemokines in IAV-infected mice, thereby reducing death.[82] Pathogenic human coronaviruses also cause a high accumulation of OxPL in patients' lung tissues, resulting in ALI.[81] Thus, it seems that eritoran and other OxPL inhibitors may also be able to alleviate HCoV-induced inflammatory responses.

Sphingosine-1-phosphate receptor 1 agonist therapy

Sphingosine-1-phosphate (S1P) is a signal lysophospholipid that promotes cytokine synthesis and secretion.[83] The S1P receptor signaling pathways significantly inhibit the pathological damage induced by the host's innate and adaptive immune responses, thereby reducing the cytokine storm caused by influenza virus infection.[84,85] In mouse models of IAV infection, sphingosine-1-phosphate receptor 1 ($S1P_1$) signal transduction in respiratory endothelial cells modulates pathogenic inflammatory responses.[85] Agonists targeting $S1P_1$ inhibit excessive recruitment of inflammatory cells, inhibit proinflammatory cytokines and chemokines, and reduce the morbidity and mortality of IAV.[85,86] SARS-CoV-2 also mainly infects human lung epithelial cells and endothelial cells. Therefore, $S1P_1$ agonists may be potential therapeutic drugs for reducing cytokine and chemokine responses in those HCoV patients whose cells generated excessive immune responses. An S1P-receptor modulating drug, siponimod, was approved in 2019 to treat multiple sclerosis. However, clinical trials are needed to further verify whether siponimod is an ideal alternative for the treatment of cytokine storm.

Stem cell therapy

As an important member of the stem cell family, mesenchymal stem cells (MSC) not only have the potential of self-renewal and multidirectional differentiation, but also have strong anti-inflammatory and immune regulatory functions. MSC can inhibit the abnormal activation of T lymphocytes and macrophages, and induce their differentiation into regulatory T cell (Treg) subsets and anti-inflammatory macrophages, respectively. It can also inhibit the secretion of pro-inflammatory cytokines, such as, IL-1, TNF-α, IL-6, IL-12, and IFN-γ, thereby reducing the occurrence of cytokine storms.[87,88] At the same time, MSC can secrete IL-10, hepatocyte growth factor, keratinocyte growth factor and VEGF to alleviate ARDS, regenerate and repair damaged lung tissues, and resist fibrosis.[89] Therefore, many functions of MSC are expected to make it an effective method for the treatment of COVID-19.

Blood purification treatments

In addition, the blood purification treatments currently used in clinic practice can remove inflammatory factors to a certain extent. Blood purification system including plasma exchange, adsorption, perfusion, blood/plasma filtration, etc., can remove inflammatory factors, block the "cytokine storm", to reduce the damage of inflammatory response to the body. This therapy can be used for severe and critical patients in the early and middle stages of the disease. The artificial liver technology led by Academician Li Lanjuan can eliminate inflammatory factors on a large scale. This technology has also been used to resist the cytokine storm of H7N9, and its application on COVID-19 has also achieved certain efficacy.[90] Early renal replacement therapy, which is similar to the treatment principle of artificial liver technology, seems to be an effective method to control cytokine storm.[91]

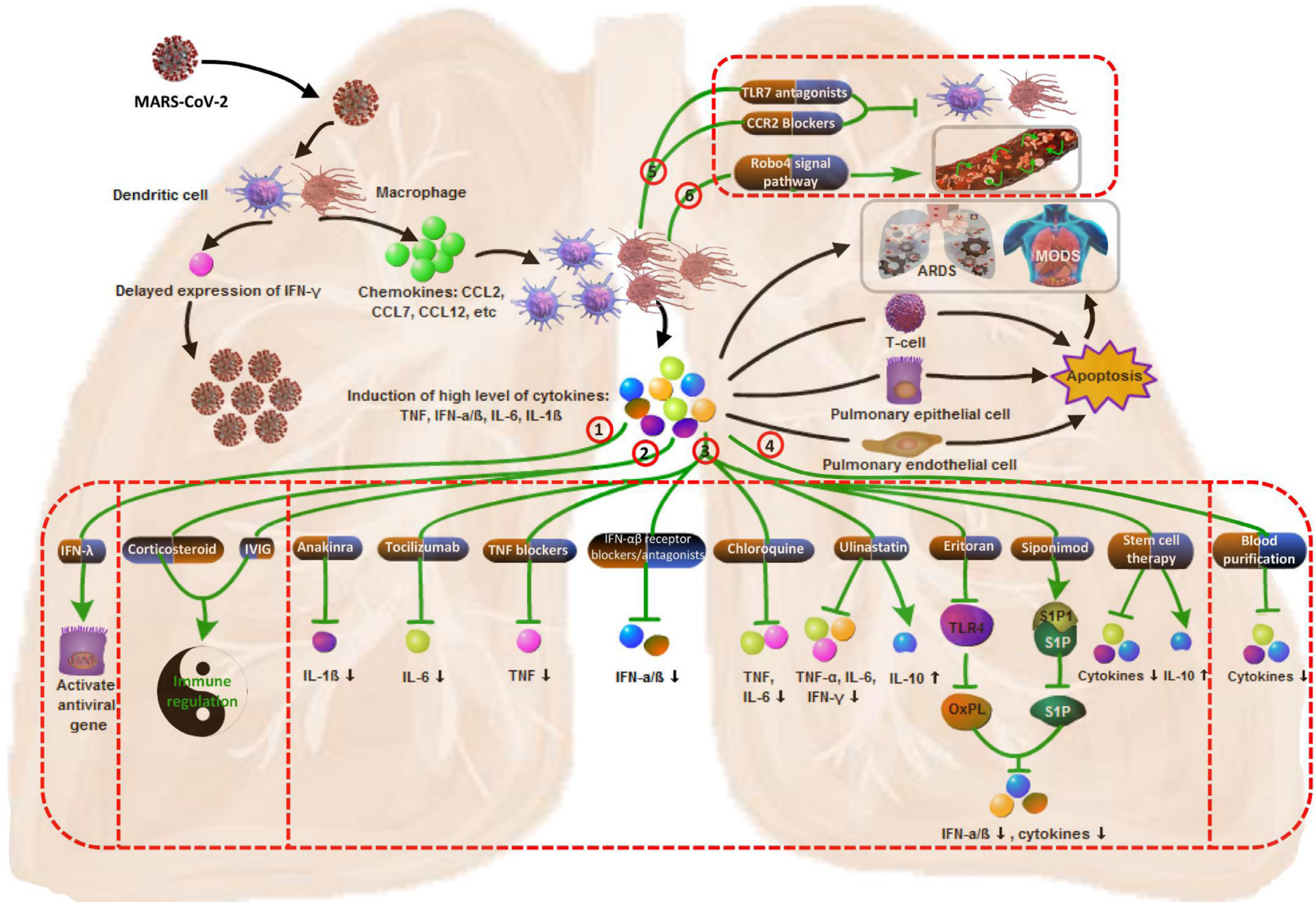

Fig. 1. Mechanism of cytokine storm in COVID-19 and potential therapy.
① Supplement with IFN-λ to activate the innate immunity; ② Using immunomodulator to restore immune balance; ③ Inhibiting the production of cytokines; ④ Scavenging cytokines; ⑤ Inhibiting mononuclear macrophage recruitment and function; ⑥ Strengthening the vascular barrier by activating of the endothelial Slit-Robo4 signal pathway.

Inhibitors of mononuclear macrophage recruitment and function

An autopsy report of patients with COVID-19 revealed a large amount of inflammatory cell infiltration in the lungs of the deceased.[92] One potentially effective treatment approach is to reduce the recruitment of mononuclear macrophages to the site of inflammation through small interfering RNA (siRNA)-mediated silencing of C-C chemokine receptor type 2 (CCR2), which has been demonstrated by animal experiments to improve the outcome of the disease.[93,94] Toll-like receptor 7 (TLR7) agonists stimulate mononuclear macrophages to undergo a strong inflammatory response at the time of infection with single-stranded RNA (ssRNA) viruses such as HCoV. Therefore, TLR7 antagonists may be able to alleviate the storm of inflammatory factors caused by SARS-CoV-2 infection.

Strengthens the vascular barrier

Increased vascular permeability is also a hallmark change that occurs in the process of a cytokine storm. It was found in animal infection models of sepsis and H5N1 virus that activation of the endothelial Slit-Robo4 pathway with drugs improved vascular permeability, thereby reducing the occurrence of a cytokine storm during infection.[95]

Conclusion

Inflammation is an essential part of an effective immune response. It is difficult to eliminate infections successfully without inflammation. The inflammatory response begins with an initial recognition of pathogens. The pathogens then mediate the recruitment of immune cells, which eliminates the pathogens and ultimately leads to tissue repair and restoration of homeostasis. However, SARS-CoV-2 induces excessive and prolonged cytokine/chemokine responses in some infected individuals, known as the cytokine storm. Cytokine storm causes ARDS or multiple-organ dysfunction, which leads to physiological deterioration and death. Timely control of the cytokine storm in its early stage through such means as immunomodulators and cytokine antagonists, as well as the reduction of lung inflammatory cell infiltration, is the key to improving the treatment success rate and reducing the mortality rate of patients with COVID-19. Fig. 1

Declaration of Competing Interest

The authors declare that they have no competing financial interests.

Contributors

QY led the writing of the manuscript. JHM developed the initial concept and framework for the manuscript and oversaw the drafting of the manuscript. All authors contributed to the content, drafting, and critical review of the manuscript.

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